The treatment of panic disorder

psychotherapy, pharmacotherapy, or the two combined?

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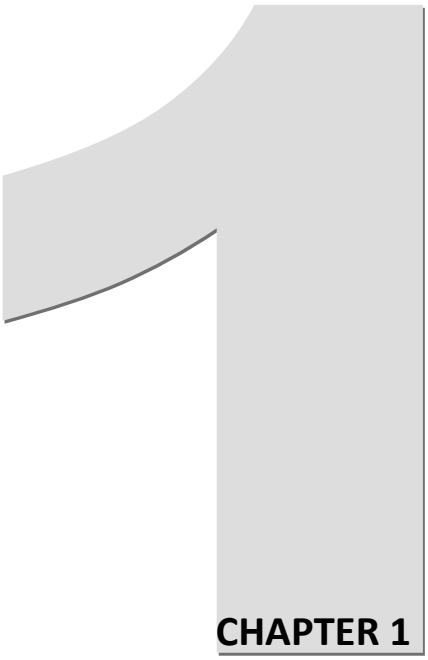
List of Acronyms:

PD	panic disorder
AG	agoraphobia
SSRI	serotonin selective reuptake inhibitor
CBT	cognitive behavioral therapy
CBT+SSRI	combined CBT and SSRI treatment
TCA	tricyclic antidepressants
ES	effect size
ITT	intent-to-treat analysis
n	number of subjects
APA	American psychiatric association
DSM	diagnostical and statistical manual of mental disorders



CHAPTER 1

GENERAL INTRODUCTION

Treating panic disorder: Update on current status

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1.1 Clinical features of panic disorder with or without agoraphobia

Fear protects us from danger by triggering an adaptive response to threat. The original formulation of the 'fight or flight response'[1] explained how the sympathetic nervous system is triggered enabling animals in potential danger to flee or fight. Physiological reactions associated with this innate fight of flight response include, among others, acceleration of heart and lung action, inhibition of stomach and upper-intestinal action, constriction of blood vessels, tunnel vision, and shaking. People who suffer from panic attacks experience similar physiological reactions but without the presence of an external threat making them extremely anxious and often catastrophizing their bodily experiences.

In distinguishing normal fear from pathological fear characterizing anxiety disorders, pathological fear is (a) excessive in relation to the situation, (b) cannot be reasoned away, (c) is beyond voluntary control, (d) leads to avoidance of the feared object or situation, (e) persists over time, (f) is maladaptive, and (g) is not age specific.(1) What was initially called 'agoraphobia with panic attacks' in DSM-III (APA, 1980) was renamed 'panic disorder with or without agoraphobia' in the DSM-III-R (APA, 1987). In the DSM-IV (APA, 1994) panic disorder (PD) is characterized by recurrent panic attacks and fear for subsequent attacks and/or their consequences (see boxes 1.1 to 1.3 for DSM-IV criteria). A panic attack is defined by a cluster of physical and cognitive symptoms and is described as a purely terrifying experience by those who go through them. Although panic attacks are common to all anxiety disorders, in PD they are mostly unexpected of without an obvious external trigger. For most PD sufferers, their first panic attack has been stamped indelibly into their memory. In order to prevent the onset of subsequent panic attacks, PD patients tend to avoid certain situations or behaviors often resulting in concurrent agoraphobia (AG) (literally referring to fear of the marketplace).

[1] Fight or flight: original formulation by Walter Cannon in 1929.

Box 1.1.

DSM-IV criteria for panic attack:

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1) palpitations, pounding heart, or accelerated heart rate
2) sweating
3) trembling or shaking
4) sensations of shortness of breath or smothering
5) feeling of choking
6) chest pain or discomfort
7) nausea or abdominal distress
8) feeling dizzy, unsteady, lightheaded, or faint
9) derealization (feelings of unreality) or depersonalization (being detached from oneself)
10) fear of losing control or going crazy
11) fear of dying
12) paresthesias (numbness or tingling sensations)
13) chills or hot flushes

Box 1.2.

DSM-IV criteria for panic disorder:

A) Both (1) and (2):

(1) Recurrent unexpected Panic Attacks
(2) At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
(a) persistent concern about having additional attacks
(b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
(c) a significant change in behavior related to the attacks

B) The Panic Attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
C) The Panic Attacks are not better accounted for by another mental disorder (e.g., social anxiety disorder, specific phobia)

In the DSM-IV, PD with AG, PD without AG, and AG without a history of PD are distinguished. Data on prevalence of these different disorders are inconclusive and there is still debate regarding the relationship between PD and AG.[2,3] Isolated panic attacks are not diagnosed as a disorder. However, they are relatively common in non-clinical populations and also frequently associated with a variety of anxiety disorders besides PD such as social anxiety disorder or specific phobias.[4]

The life-time prevalence rates for PD with or without AG fluctuate between 2% and 4%[5,6] with a recent study in the United States reporting a life-time prevalence of 3.8%.[7] In the Netherlands, a lifetime prevalence of 3.8% was found as well.[8] Most studies reporting on PD consistently show higher rates for women than for men.[4] PD typically runs a chronic course[9,10] and is associated with substantial reduction in quality of life.[11,12]

Box 1.3.

DSM-IV criteria for Agoraphobia:

A) Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed Panic Attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd, or standing in a line; being on a bridge; and traveling in a bus, train, or automobile.
B) The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a Panic Attack or panic-like symptoms, or require the presence of a companion.
C) The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as Social Phobia (e.g., avoidance limited to social situations because of fear of embarrassment), Specific Phobia (e.g., avoidance limited to a single situation like elevators), Obsessive-Compulsive Disorder (e.g., avoidance of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), or Separation Anxiety Disorder (e.g., avoidance of leaving home or relatives).

1.2 Understanding panic disorder: Onset and maintenance

Throughout the years, several models explaining the origins of PD have been developed. Traditionally, the biological view has been predominant but in the 1980s psychological theories became increasingly influential. Since the late 1990s, the biological and psychological viewpoints have started to merge, making room for an integrated viewpoint on the origins and workings mechanisms involved in PD. A stress-diathesis model is most commonly used to explain the genesis and maintenance of PD in which an interaction between life stress and genetic susceptibility is proposed as being the root cause of PD. The concept of anxiety sensitivity [13,14] may help in understanding why some individuals respond different than others to the bodily sensations associated with anxiety. When fear of fear develops, initial panic attacks may spiral into PD. With the onset of the disorder, changes in the neural circuits of the brain of patients with PD (emphasizing the role of the amygdala and related structures) are thought to play a role in the maintenance of the disorder as well as cognitive factors such as interoceptive conditioning.[15]

1.3 The context-safety hypothesis

Contemporary learning theory is consistent with data supporting cognitive theories emphasizing catastrophic misinterpretations [e.g.16] and stresses that catastrophic cognitions can be seen as a part of 'context' or constellation of cues that have been linked to panic.[17] Understanding the role of context is important in predicting the return of fear and anxiety often observed in PD.[18] It is suggested that patients receiving CBT have tested and disconfirmed their feared catastrophes regarding feared bodily sensations (through interoceptive exposure) and feared situations (through exposure in vivo). In this way, a sense of safety is relearned. When this

relearning of safety is context dependent, there are some implications for clinical treatment. For CBT this means that conducting exposure in multiple contexts is important. Regarding medication treatment, it is important to realize that internal states are also considered to be part of context.[17,19-23] A mismatch of internal state during treatment (while on medication) and follow-up (after tapering medication) may result in fear renewal.[18,24] In the present thesis, there will be referred to this hypothesis as the 'context-safety hypothesis'.

1.4 Interventions

In clinical practice today, PD is mostly treated with some form of either a psychopharmacological treatment, most often with a Serotonin Selective Reuptake Inhibitor (SSRI), or with a psychological treatment, most often cognitive behavioral therapy (CBT). Besides offering either CBT or an SSRI, the combination of these two treatment modalities appears to be common place in today's clinical practice as well. In the following paragraphs, these different treatment modalities are introduced and empirical data on treatment effectiveness is reviewed.

1.4.1 Treating PD today: SSRIs

Discovered in the late 1950s, benzodiazepines have been the mainstay in the treatment of panic disorder for decades.[25] Initial enthusiasm waned due to observations of risks on over-sedation, cognitive impairment, long-lasting withdrawal symptoms and dependence. The first antidepressants that were found to be effective for PD were tricyclic with imipramine and clomipramine being most investigated.[26] Although proven efficacious, the side effect profile of this class of drugs limits the more widespread use of tricyclic antidepressants (TCAs).[27] At the end of the 1980s and throughout the 1990s, more and more studies were performed

on the effects of a new class of psychotropic drugs, the SSRIs. The first SSRI to be indicated for use in treating PD was paroxetine in 1989[28] which was later accompanied by fluoxetine, sertraline, fluvoxamine, and citalopram. At present, SSRIs are considered as first-line pharmacotherapy agents for PD[29] due to their overall levels of efficacy, safety and tolerability.[26,29,30]

The specific mechanism of action of the SSRIs is not entirely clear.[31] It is suggested that a dysfunction of serotonin neuronal pathways may mediate PD. Consequently, antidepressants that modulate serotonergic systems may be effective in treating PD. SSRIs enhance serotonergic transmission by blocking the presynaptic active membrane transport mechanism for the reuptake of serotonin and consequently increases serotonergic activity at the postsynaptic receptor resulting in increased overall levels of brain 5-HT.[31,32] The 'selective' quality of the SSRIs stems from their high affinity to serotonin uptake sites, low affinity to noradrenaline uptake sites, and very low affinity for neurotransmitter receptors.[33]

A potential drawback of the SSRIs is the delayed response treatment effect; it takes approximately three to eight weeks before benefit may be noticed. Also, starting doses should be low and the doses should be increased slowly because panic symptoms may be exacerbated when the starting dose is too high.[34,35]

Compared to other psychotropic drugs, SSRIs exhibit a low side-effects profile.[36] Mostly reported side effects by patients receiving SSRIs include sweating, diarrhea, nausea, jitteriness, headaches, dizziness, and abnormal ejaculation or anorgasmia.[26,28,37] Regarding the length of treatment, most clinicians recommend continuing treatment at least 6 months to 1 year after recovery[38] although there is clearly a lack of studies into this matter.[27]

As with any pharmacological agent, the discontinuation of an SSRI may cause patients to experience time-limited withdrawal symptoms[39] which could be an interoceptive stimulus that triggers or contributes to PD relapse.[15,40] Frequently reported withdrawal symptoms include dizziness, light-headedness, insomnia,

fatigue, anxiety, agitation, nausea, headache, and sensory disturbance. It must be noted that the different SSRIs seem to have somewhat different side-effects profiles and may present patients with different withdrawal symptoms as well. To prevent withdrawal symptoms, a gradual taper is recommended.[34]

Not all patients remain symptom free following medication taper. However, studies presenting relapse rates after SSRI discontinuation are scarce. Most studies on the subject of relapse deal with other (and older) pharmacotherapeutical agents such as benzodiazepines or tricyclic antidepressants. As one expert states "the systematic study of the outcome of pharmacological treatment in a naturalistic setting of routine pharmacological clinical care is a poorly funded area" (pp 127).[41]

1.4.2 Treating PD today: CBT

Up to the early 1980s, CBT for PD with AG emphasized in vivo exposure strategies targeting agoraphobic avoidance (in accordance with the formulation in the DSM-III (1980) in which the disorder was named 'agoraphobia with panic attacks').

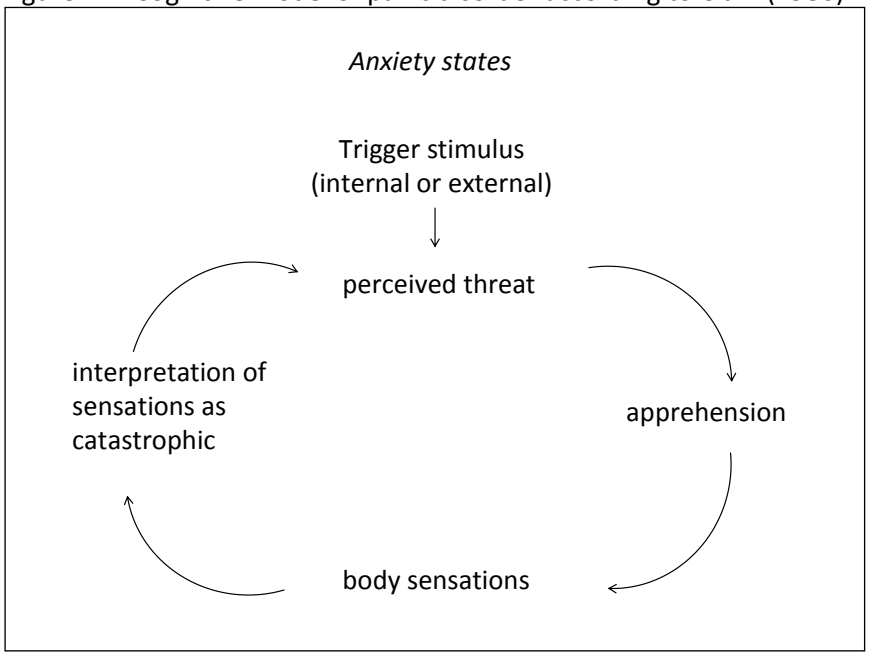
The cognitive component received more attention in the 1980s as the cognitive theory of PD was developed by researchers such as Clark[16] and Beck.[42] It proposes that patients suffering from panic attacks interpret bodily sensations in a catastrophic way. The interaction of symptoms and interpretations of these symptoms produces a vicious circle leading up to a panic attack. This cognitive theory proved fruitful and yielded new applications for treatment. These new developments resulted in a shift within the field of CBT throughout the 80s from behavioral techniques targeting agoraphobic avoidance to behavioral and cognitive techniques targeting panic attacks directly.

Two important treatment protocols both framed within the cognitive behavioral model are the panic control treatment developed by Barlow, Craske and co-workers[43-45], and the cognitive therapy by Clarks research group.[16,46] In practice, the

similarities between these protocols are probably greater than their differences. In the approach by Barlow the emphasis is on the interoceptive sensations while in the approach by Clark the emphasis is more on the erroneous cognitions.[47]

Controlled clinical trials evaluating cognitive-behavioral approaches for PD have accumulated during the last two decades. CBT is generally considered to be a cost effective treatment, is not associated with side effects[2], and is seen as durable with patients needing no additional treatment after completion and low relapse rates.

Figure 1.1. Cognitive model of panic disorder according to Clark (1986)



In recent years, attempts have been made to improve accessibility to CBT by delivering CBT in a brief format [e.g. 48,49], in groups[e.g. 50-52], online[e.g. 53], or as self-administered variant.[54] In reviewing the existing evidence for the efficacy of CBT, it should be noted that different treatment protocols are applied in different studies with subtle of less subtle differences in treatment focus. Common techniques in CBT

[2] Although we are not aware of any studies inquiring side effects in patients receiving CBT

treatment protocols include psycho-education, cognitive restructuring, breathing retraining, interoceptive exposure, and exposure in vivo or situational exposure. A meta-analysis evaluating different CBT techniques found the combination of exposure and relaxation and/or breathing retraining to be most beneficial for PD patients.[47] In the same line of research, behavioral experiments, considered a cognitive strategy, were found to be adding to the effect of exposure alone.[55] Regarding treatment length, most protocols consist of 12 to 16 sessions although shorter durations have also been reported.[49] In general, the focus of CBT treatment is the present, not the past. Also, CBT is directly aimed at the complaints as experienced by patients in their daily lives. Finally, CBT relies on an active attitude of patients expecting them not only to be actively involved during sessions, but also at home by doing homework assignments. In a meta-analysis, the latter has been shown to improve benefits of treatment.[47]

1.4.3 Treating PD today: Combined treatments

In clinical practice in the Netherlands, PD sufferers are regularly being prescribed medication by their general practitioner. When symptoms do not remit, patients may subsequently be referred to a general health clinic where they might be offered additional CBT. The reversed order (first CBT, than additional SSRI) is also encountered but probably somewhat less frequent. Besides adding one modality to the other, both treatment modalities can also be offered together as an integrated approach.

Delivering both CBT and pharmacotherapy as an integrated approach might facilitate both treatment modalities. CBT might be facilitated by adding pharmacotherapy because the medication might elevate mood, improve self-directed exposure, and enhance self-appraisal of accomplishments. In turn, pharmacotherapy might be facilitated by adding CBT with respect to medication

acceptance, tolerance of side-effects, tolerance or relieve of withdrawal, and prevention of relapse.[24] Next to possible advantages of combining treatments, there are also concerns. For instance, some experts believe that medication interferes with CBT by blocking physical fear reactions and thereby preventing patients to disconfirm erroneous cognitions.[56] It is important to note that although combined treatment seems commonly recommended and is by some thought to facilitate both individual modalities; empirical support for the combined treatment is limited.[56] There is a clear lack of studies comparing monotreatments to the combined treatment (see also paragraph 1.4.4) with respect to short and especially long-term effectiveness. Other significant issues awaiting further investigation relating to the integrated approach include the optimal sequencing of treatments, the optimal duration of medication with respect to CBT, the optimal duration of CBT with respect to medication, and treatment rationales offered to patients and its relation to outcome.

1.4.4 General considerations on treatment allocation and patients' preferences

With more than one effective treatment modality being available, mental healthcare professionals might apply some general considerations in treatment allocation. They may consider one treatment modality more suitable for a particular patient than another based on clinical experience. Also, patients themselves might come to the treatment clinic with expectations concerning different treatment modalities. Empirical data underpinning treatment allocation is scarce however. There are some indications that patients prefer cognitive coping strategies over taking medication[57] but on the whole, little is known about patients' preferences. Little is also known about the influence on outcome of treatment allocation based on preference. One study comparing PD patients treated with cognitive therapy by allocation and patients treated by preference did not find evidence for a moderating effect of

preference on treatment effect.[58]

Next to preferences patients might have beforehand, there is also a paucity of research on patient satisfaction after completing treatment. In a study comparing group behavior therapy and telephone behavior therapy for PD with AG, patients completed a satisfaction questionnaire which asked patients whether they found various treatment components useful. Also, ratings of 'liking' were collected for each component.[59] For self-directed in vivo exposure, usefulness ratings were significantly higher than 'personally liked' ratings. For psycho-education, usefulness and liking ratings were both high. We found no studies evaluating patients' satisfaction following a pharmacological treatment and no data on the comparison between psychological and pharmacological treatments regarding treatment satisfaction.

In general, the following considerations might be important in treatment allocation from the patient's perspective. Patients having received CBT often experience a sense of control over their complaints that was not present before. Also, CBT patients might derive a sense of satisfaction from the fact that they themselves have been able to tackle their fears. After treatment completion they often feel confident about their ability to cope with possible future complains. A potential drawback of CBT is its intense and time consuming nature. Patients are expected to exercise not only during treatment sessions but also outside of the clinic in their daily lives. Some patients experience CBT as difficult because they feel confronted with various personal issues they had not foreseen.

The greatest advantage of pharmacotherapy is probably the fact that patients almost effortlessly reach a better level of functioning. This treatment does not make heavy demands on patients; it is easy and costs little time. Patients might still experience physical symptoms resembling panic but actual panic attacks might cease to occur. In general, patients feel less anxious. This might give them confidence and enables them to encounter situations and places they previously avoided because of

fear of subsequent panic attacks. A potential drawback of SSRI treatment is that an SSRI needs time to kick-in (on average: three to eight weeks) while patients often long for immediate relief. Also, during the first weeks of the SSRI use, patients often experience side effects, including elevated levels of anxiety, which usually abate as treatment continues. Other side effects however, may persevere while continuing treatment, for instance regarding sexual dysfunction. Women who experience panic complaints and who wish to become pregnant in the nearby future may for this reason feel reluctant to start pharmacotherapy. An often heard concern of patients is the fear of becoming dependent on medication. Another potential drawback is that some patients suffer from treatment adherence problems for instance because of trouble remembering to take medication on a daily basis. Also, once patients experience a relief from their complaints, they sometimes dread medication taper. Many patients express the fear that complaints will return after tapering medication. This problem should be tackled by providing clear information about what might be expected during and after medication taper.

The rationale that patients receive may also contribute to treatment satisfaction and possibly to treatment outcome. Patients receiving CBT are basically explained that panic attacks result from catastrophic misinterpretations of harmless bodily sensations. With pharmacotherapy, patients are usually explained that panic attacks result from a central neurochemical abnormality which causes the body's 'alarm system' to be hypersensitive and pharmacotherapy should corrects this abnormality. Patients about to receive CBT might like the idea of controllability that is included in the CBT rationale. Patients about to receive SSRI might like the idea that it is not their fault that they experience these complaints; there is an identifiable cause outside of their control. Interestingly, patients receiving both CBT and SSRI might receive both rationales. The importance of these rationales and their possible influence on treatment effect has not been subject to research to date but might be an important issue in future studies, especially with respect to the combined

treatment. Data on attribution of effect might also gain insight in this matter: little is yet known about to which treatment modality patients attribute reached gains when receiving both CBT and SSRI.

In conclusion, more research is needed on the subject of treatment preference, treatment satisfaction, and on how patients explain possible improvement in relation to the treatment rationale they received.

1.4.5 Treatment guidelines

Multidisciplinary treatment guidelines for mental health care in the Netherlands were developed from 2001; these guidelines are based on scientific data gathered in reviews and meta-analyses, and consensus when empirical data is lacking. The first Dutch treatment guidelines for anxiety disorders were finally published in December 2003. For the present study however, patients were enrolled between April 2001 and September 2003.

The following text is based on the latest revision of the guidelines which was published in 2009.[60] Regarding psychotherapy, exposure in vivo is recommended for PD patients with AG while panic management is advised when avoidance behavior is absent or limited. In the guidelines, panic management refers to different interventions such as coping, offering alternative and reassuring explanations for experienced symptoms, and interoceptive exposure. The panic control treatment (see section 1.4.2) is mentioned as an example of a panic management protocol. With respect to pharmacotherapy, SSRIs are considered the first treatment of choice. Benzodiazepines should only be considered as a later step in pharmacotherapy and only if CBT has been offered prior. Further, benzodiazepines may be used temporarily if starting an SSRI causes initial higher anxiety levels. Only for patients with a co-morbid severe depression, pharmacotherapy is advised as first-step treatment. When depressive symptoms start to wane, additive CBT may be started.

In the guidelines, a distinction is made between mild PD and severe PD. Other than suggesting that concurrent AG may affect the severity of the PD, no criteria for mild or severe PD are proposed however. Regarding treatment, it is suggested that in case of mild PD, CBT should be offered first before considering pharmacotherapy.

From a stepped-care perspective, the following algorithm is presented for severe PD with or without AG (because SSRIs are considered first choice, we will write SSRI in stead of pharmacotherapy):

1. First step interventions (e.g. psycho-education, (computerized) self-help, counseling).
2. Either SSRI or CBT. This choice can be made by the caregiver (e.g. therapist) and patient together. Evaluate after twelve weeks. If CBT is successful: relapse prevention and completion of treatment. If SSRI is successful, continue for one year, than offer relapse prevention and gradually taper. If SSRI is not successful: taper and subsequently start CBT. If CBT is not successful: end treatment and subsequently start pharmacotherapy. If CBT or SSRI remission is partial, go to step 3:
3. Add pharmacotherapy to ongoing CBT of add CBT to ongoing pharmacotherapy.

The combined treatment is thus considered the next step in treating PD when monotreatment has been only partially successful. Note that in the guidelines, the presence or severity of AG may be of influence regarding choosing psychotherapy (e.g. exposure in vivo or panic management) and may partially influence the severity of the PD but in itself has no place within the proposed algorithm.

1.5 Empirical Studies

Hereafter, we provide a review of empirical studies on the treatment of PD with or without AG with an emphasis on evidence derived from randomized controlled trials. It must be noted that PD has enjoyed considerable attention in the literature since its introduction in the DSM-III. We have limited our review by focusing only on studies investigating CBT and / or SSRI in the treatment for PD with a special interest in studies comparing these monotherapies to the combination of both (see sections 1.5.1 through 1.5.5). Of further interest was data on cost-effectiveness of PD treatments (1.5.6) and conclusions regarding treatments for PD derived from several meta-analyses (1.5.7).

1.5.1 Cognitive behavioral therapy

A number of studies established the superiority of cognitive behavioral treatments over no treatment waiting-list, a psychosocial placebo, or a pill placebo (for reviews on the effectiveness of CBT see[44,47,61,62]). There is also some evidence for superiority over other active treatment modalities such as medication. To highlight a few individual studies; CBT was compared to a control group[63] and after six weeks CBT superiority was established. When compared to applied relaxation and imipramine,[64] cognitive therapy was superior to both relaxation and imipramine after the acute treatment phase of three months. At 15-month follow-up, cognitive therapy was again superior to both applied relaxation and imipramine. CBT was compared to medication (the benzodiazepine alprazolam), pill placebo and waiting list control[65] and results indicated that CBT significantly outperformed the latter two. Another study also applying the panic control treatment[45] found this treatment protocol as effective as panic control combined with in vivo exposure.

With respect to long-term effectiveness, Brown et al.[66] reported that 47.6% of

patients having received CBT and seen for a 24-month follow-up still met criteria for high end-state functioning and had sought no further treatment during the follow-up period. Results suggested that PD patients treated with CBT do reasonably well over the long term but still suffer from periods of exacerbation of their PD. In another study three CBT modalities, standard, group, and brief CBT, were compared[67] and results indicated a maintained beneficial effect of all modalities at a two-year naturalistic follow-up. It must be noted however that in this study, patients were allowed concurrent anxiolytic or antidepressant medication.

1.5.2 SSRI treatment

A substantial body of research on the effectiveness of SSRIs is currently available.[68] Reported studies differ regarding several aspects e.g. patient samples, medication dosages, outcome measures, and design (e.g. whether or not double-blind). Overall, SSRIs are considered effective agents in the acute treatment of PD.[69-71] Less clarity exists regarding the issue of using SSRI as maintenance therapy[72] and regarding relapse after treatment discontinuation. In the present thesis the following five SSRIs were evaluated, with references of published general reviews on these agents between brackets: fluoxetine[73], paroxetine,[31,74] fluvoxamine,[75] sertraline,[76] and citalopram.[77]

Regarding the treatment of PD, especially the evidence for short term effectiveness is robust (paroxetine:[34,78], fluvoxamine:[79-83], fluoxetine:[84-86], sertraline:[87-89], citalopram:[90]).

Long-term studies are essential but are nevertheless conducted less frequently.[91] Lecrubier et al.[92] extended their 12-week study on the effects of paroxetine with another 36 weeks and found efficacy maintained. In another maintenance study, the continuing effect of paroxetine (as compared to clonazepam) was studied for a total of three years and effects were found to be

maintained.[93] In the same line of research, Schneier et al.[94] report on a 12- month study on fluoxetine and found that 67% of the patients reported moderate to marked improvement. Another one-year study[95] established good results for citalopram, as compared to clomipramine, a TCA. These results were subsequently replicated.[96]

Next to long-term effectiveness studies, there is also a need for studies on the effect of maintenance after tapering. Patients who had been treated for sertraline for a year were subsequently randomized to continue sertraline for 28 weeks or to switch to placebo for 28 weeks.[97] Significantly more patients experienced an exacerbation of panic symptomatology in the placebo group (33%) as compared to the sertraline group (13%). It was concluded that continuing sertraline prevented relapse. In a three year naturalistic outcome study using paroxetine[98] patients who had been on maintenance therapy for twelve months were given the choice to continue or taper and both groups were monitored. Only 14% of the patients who had discontinued medication relapsed during the follow-up phase. Note that patients were not randomized at random but by preference.

1.5.3 Monotherapies compared: SSRI-only vs. CBT-only

Black et al.[99] randomly assigned 75 patients to receive cognitive therapy (CT), fluvoxamine, or placebo for eight weeks. Significant differences favoring fluvoxamine over placebo were observed at almost each week of the trial and for most outcome variables. CT was superior to placebo on some measures but not all. CT was not superior to fluvoxamine on any measure.

Bakker et al.[100] compared the relative efficacy of paroxetine, clomipramine (a TCA), placebo, and cognitive therapy in 131 PD patients. After 12 weeks, 37% of the patients treated with pill placebo, 59% of the patients treated with clomipramine, 54% of the patients treated with CT, and 75% of the patients treated with paroxetine

were free from panic attacks. CT treatment yielded significant advantages over placebo only on two measures: panic frequency and patient global evaluation. As noted by the authors, the effects of CT fall behind those of most other controlled studies on the efficacy of CT for PD. This might be explained by the fact that, in contrast to other studies[e.g. 101] severe agoraphobia was allowed. Also, the duration of PD was longer as compared to patient samples in other studies.

1.5.4 Combining treatments: SSRI use in the context of CBT and CBT use in the context of SSRI

Apart from controlled studies investigating the differential effects of pharmacotherapy and CBT, five (mostly clinical case) studies were reported on in which CBT and SSRI were added in the context of the other. A group-CBT was offered to 24 pharmacotherapy non-responders[102] who achieved significant clinical gains after twelve weeks. Schmidt et al.[103] investigated whether providing CBT to 22 patients currently using antidepressants would facilitate these patients tapering their medication and reported that discontinuation in the context of CBT did not produce the adverse withdrawal symptoms that usually occur when tapering medication. A no discontinuation group without CBT was included in the design. In the same line, in a study by Whittal et al.[40] PD patients using an SSRI successfully discontinued SSRI treatment while receiving group CBT.

A related study investigated the possible benefits of adding an SSRI to a very brief CBT.[104] Two groups of PD patients, one receiving placebo, the other paroxetine, received brief CBT and it was concluded that adding an SSRI to very brief CBT failed to improve outcome.

Patients who had not responded to CBT were randomized to receive additional paroxetine next to continued CBT or additional placebo next to continued CBT.[105] Patients in the first group improved significantly on anxiety discomfort and

agoraphobic behavior while patients in the latter group did not.

In summary, pharmacotherapy nonresponders responded well to group CBT.[102] Further, CBT nonresponders responded well to an SSRI addition.[103] Also, CBT seemed to facilitate SSRI tapering.[40,103] Finally, adding an SSRI had no beneficial effect in patients who responded well to very brief CBT.[104]

1.5.5 Combining treatments: Studying different treatment modalities within one design

Studies investigating a combined SSRI and CBT treatment package for PD with or without AG are scarce. In this section, we intended to only include studies which employ a combined CBT+SSRI treatment and both monotreatments. Only two of the studies described in this section however meet this criterion: Sharp et al.[106] and Azhar et al.[107] with the latter study providing too little information regarding methodological aspects to validly interpret the results. In Table 1.1, these two studies are included together with several other studies investigating a combined pharmacotherapy and CBT treatment modality. Note that in the Barlow et al. study, a TCA rather than an SSRI was investigated. Other differences between studies listed in Table 1.1 concern methodological aspects like different inclusion criteria (e.g. level of agoraphobia, additional benzodiazepines), applied treatment protocols, and treatment setting.

Oehrberg et al.[108] found the combination of paroxetine and cognitive therapy to be more effective as compared to the combination of placebo and cognitive therapy for PD patients with or without AG who first had received a placebo for two weeks.

De Beurs et al.[109] compared five treatment groups and found the combined fluvoxamine and exposure group to be most effective after twelve weeks of treatment. Subsequently, a naturalistic follow-up was conducted after two years.[110]

Of the patients randomized in the original study to receive fluvoxamine, about 50% had been able to both taper medication and remain free of panic complaints. Patients in all treatment groups had further improved as compared to treatment endpoint and the superiority of the combined fluvoxamine and exposure group was no longer observed at follow-up.

Sharp et al.[106] enumerate five methodological weaknesses observed in treatment outcome studies on PD performed up to the middle nineties. A first point of consideration concerns the fact that most studies did not require patients receiving CBT to be medication-free. Secondly, most studies employed a psychological-treatment-plus-placebo-treatment group instead of a psychological-treatment-only group. The assumption here is that the first treatment is functionally equivalent to the latter. Since no evidence is present to confirm this assumption, studies should employ a psychological-treatment-only group as well. A third point of consideration concerns the lack of control for therapist contact. According to the authors, therapist contact time should be balanced in the psychopharmacological and psychological treatments in order to adequately compare these treatment modalities. Finally, most outcome studies were conducted in specialist clinics or hospital settings. To answer the question of practical utility and clinical applicability, studies should be conducted in the primary care setting.

In an attempt to correct the above-mentioned methodological flaws, Sharp and colleagues conducted a study in which five treatment groups were employed: fluvoxamine, placebo, CBT, fluvoxamine plus CBT, and placebo plus CBT. At end point, day 84, no significant differences were found between any of the active treatment groups (placebo thus not included). However, the results for the CBT groups seemed more robust than for the fluvoxamine groups. Six months after completing CBT and after discontinuing fluvoxamine, patients were re-assessed.

Table 1.1. Overview of studies comparing combined SSRI and CBT treatment to monotreatment(s)

Authors (year of publication)
Oehrberg et al. (1995)
Subjects
n = 120, DSM-III-R, PD with or without AG
Duration of treatment
12 weeks
Treatment modalities
1. P followed by paroxetine + CT followed by P
2. P followed by P + CT followed by P
Main ingredients of treatments
Paroxetine: titrated upwards to max 60 mg/day. No taper but switch to P after twelve weeks.
Main results
1 > 2
Follow-up (duration and results)
No follow-up
Remarks
- No information is provided regarding the contents of CT
- Paroxetine was not investigated as monotreatment
- C(B)T was not investigated as monotreatment

Authors (year of publication)
De Beurs et al. (1995)
Subjects
n = 88, DSM-III-R PD with moderate or severe AG
Duration of treatment
12 weeks
Treatment modalities
1. fluvoxamine followed by EIV
2. P followed by EIV
3. PPM followed by EIV
4. EIV
Main ingredients of treatments
- Fluvoxamine: titrated upwards to 150 mg/day. No taper.
- PPM: presenting a cognitive model of panic, hyperventilation provocation, respiratory training.
- EIV: gradually prolonged self-exposure in vivo
Main results
- 1 > 2, 3 and 4
- 2 and 3 ≈ 4
Follow-up (duration and results)
see De Beurs et al 1998
Remarks
Fluvoxamine was not investigated as monotreatment

Table 1.1. continued. Overview of studies comparing combined SSRI and CBT treatment to monotreatment(s)

Authors (year of publication)
De Beurs et al. (1998)
Subjects
n = 71
Duration of treatment
see De Beurs et al. 1995
Treatment modalities
see De Beurs et al. 1995
Main ingredients of treatments
see De Beurs et al. 1995
Main results
- Between 61 and 67% of Pt panic free
- No significant changes between groups
- 51% recovered, 25% reliably changed, 24% unchanged
- 77% received some form of additional treatment. Pt having received 1 required the least aftercare
Follow-up (duration and results)
2 year naturalistic FU
Remarks /

Authors (year of publication)
Sharp et al. (1996)
Subjects
n = 190, DSM-III-R PD with or without AG
Duration of treatment
13 weeks
Treatment modalities
1. fluvoxamine
2. P
3. fluvoxamine + CBT
4. P + CBT
5. CBT

Main ingredients of treatments
- Fluvoxamine: fixed dosed, titrated upwards to 150 mg/day. Discontinued without taper at day 84.
- CBT: Mainly exposure but no interoceptive exposure.
Main results
- 3 > 1, 2, 4, and 5 on rate of panic free Pt
- 1 ≈ 3 ≈ 4≈ 5 on other measures
- on CSC: 3 and 5 > 2 and 4

Table 1.1. continued. Overview of studies comparing combined SSRI and CBT treatment to monotreatment(s)

Follow-up (duration and results)
- FU at 6 months
- Highest number of Pt who did not receive treatment during FU: 3
- 3, 4 and 5 > 1 and 2 on CSC

Remarks
- A single therapist treated all Pt
- Only Pt without additional treatment during FU were included in analyses

Authors (year of publication)
Stein et al. (2000)

Subjects
n = 33, DSM IV PD with or without AG

Duration of treatment
10 weeks

Treatment modalities
1. very brief CBT + placebo
2. very brief CBT + paroxetine

Main ingredients of treatments
- Paroxetine: max 60 mg/day. No taper.
- Very brief CBT: 3 sessions and self-help book

Main results
2 > 1 except on panic free status

Follow-up (duration and results)
No FU

Remarks
- Pilot study
- Only two CBT therapists
- CBT was not investigated as monotreatment
- Paroxetine was not investigated as monotreatment

Table 1.1. continued. Overview of studies comparing combined SSRI and CBT treatment to monotreatment(s)

Authors (year of publication)
Azhar et al. (2000)
Subjects
n = 66, DSM IV PD
Duration of treatment
9 weeks
Treatment modalities
1. CBT
2. CBT + fluvoxamine
3. fluvoxamine

Main ingredients of treatments
- Fluvoxamine: max 200 mg/day. No taper.
- CBT: according to Clark.

Main results
1 and 2 > 3
Follow-up (duration and results)
No FU
Remarks
- No information regarding AG status
- Methodological information very limited

Authors (year of publication)
Barlow et al. (2000)
Subjects
n = 312, DSM-III-R PD with or without mild AG
Duration of treatment
For all Pt: 3 months. For responders: 9 months
Treatment modalities
1) CBT
2) imipramine
3) P
4) CBT + imipramine
5) CBT + P

Main ingredients of treatments
- Imipramine: max 300 mg/day. Taper (1-2 weeks) after 9 months.
- CBT: interoceptive exposure, cognitive restructuring and breathing retraining.

Main results
- 1 and 2 > 3
- among responders: 2 produced higher quality of improvement
- 4 confers limited advantages acutely but at end of maintenance: 4 > 1 and 5

Table 1.1. continued. Overview of studies comparing combined SSRI and CBT treatment to monotreatment(s)

Follow-up (duration and results)
- Fu at 6 months
- 1 and 5 > 3
- 2 and 4 ≈ 3
- Highest relapse rate for 4
Remarks
- Imipramine is not an SSRI
- Moderate or severe AG excluded

Abbreviations: PD = panic disorder, EIV = exposure in vivo, B = benzodiazepines, n = number of participants at start treatment, Pt = patients, AG = agoraphobia, CBT = cognitive behavioral therapy, P = placebo, PPM = psychological panic management, FU = follow-up, CSC = clinically significant change, CT = cognitive therapy, > outperformed, ≈ no significant differences.

Of the patients who had received no additional treatment during follow-up, the proportion of patients achieving clinically significant change was consistently higher for the groups which received psychological treatment (fluvoxamine plus CBT, placebo plus CBT, and CBT alone) as compared to the medication-only groups (fluvoxamine and placebo).

In sum, results showed that fluvoxamine produced considerable gains but there was a fall-off in these gains over follow-up. CBT also produced gains and these were better maintained over follow-up. There was some evidence that improvement was more rapid in the combined CBT and fluvoxamine group as compared to CBT alone. The generalizability of results is restricted due to the fact that only a single therapist performed all treatments. Also, the fact that patients in all treatment groups received an equal amount of treatment sessions and the same amount of therapist contact time jeopardizes generalizability to clinical practice. In clinical practice, patients receiving medication generally spent less time with their pharmacotherapist as compared to the time that patients receiving CBT spent with their therapist.

In a study by Azhar et al.,[107] CBT and CBT combined with fluvoxamine outperformed fluvoxamine-only after nine weeks but as stated, too little information regarding important methodological aspects is provided. A study comparing very brief CBT + paroxetine to very brief CBT + placebo established superiority of the first

over the latter.[104]

A large randomized trial was conducted by Barlow and colleagues.[101] Patients were randomly assigned to receive imipramine, CBT, placebo, CBT plus imipramine, or CBT plus placebo. Although imipramine is not an SSRI but a TCA, the study is included in this section because it is well-designed, involved a large study sample and because there is some evidence to suggest that the effect of a TCA may be more or less comparable to those of the SSRIs. The total study duration was fifteen months, consisting of an acute treatment phase of three months, a maintenance phase of six months, and subsequently a follow-up phase of another six months. During the acute treatment phase, CBT patients received eleven 50-minute sessions. Patients receiving imipramine visited their pharmacotherapist eleven times as well. During the maintenance phase, treatment was continued on a monthly basis. Responders to these nine months of treatment then discontinued the treatments and were assessed again six months later. Medication was discontinued after nine months of treatment by tapering during a one- to two-week period.

Results indicated that both imipramine and CBT were more effective in treating PD than placebo. After nine months, imipramine had produced a superior quality of response in imipramine responders as compared to the quality of the response to CBT in CBT responders. At follow-up, CBT proved to have more durability. A 4% relapse was observed for patients who had received CBT, compared to a 25% relapse for patients who had received imipramine. Also, CBT seems to be somewhat better tolerated. Acute co-administration of imipramine and CBT resulted in limited benefit over monotherapy, so a surplus value of a combined therapy was, as in the Sharp study, not established. Also, the addition of CBT did not mitigate relapse following medication discontinuation.

A limitation of the Barlow et al. study is that patients with severe agoraphobia were excluded. Results are thus only generalizable to patients with no or mild agoraphobia.

1.5.6 Meta-analytic reviews

Several meta-analytic reviews have compared psychopharmacological, cognitive behavioral and combined treatment packages for PD with or without AG.[62,69,111] An overview of meta-analyses is presented by Mitte.[69] As she points out, several methodological problems associated with meta-analyses limit the validity of results. In an attempt to overcome these problems a random effects-model was applied in a meta-analysis including 124 studies.[69] Results of this meta-analysis suggested that in the aggregate, CBT was equally or sometimes more effective as pharmacotherapy. No significant differences between CBT as monotreatment and CBT combined with pharmacotherapy were found.

The most recent meta-analysis that was published[112] included 21 randomized trials investigating the effects of (combined) psychotherapeutical and pharmacotherapeutical treatments for PD with or without AG. Psychotherapeutical treatments included behavior therapy, cognitive therapy, a combination of cognitive and behavior therapy, or other psychotherapy. Pharmacotherapeutical treatments included administering tricyclic antidepressants, SSRIs and monamine oxidase inhibitors. Results indicated that in the acute treatment phase, the combined treatments was 1.24 times more likely to produce a response compared to pharmacotherapy as monotreatment and was 1.6 times more likely to produce a response compared to psychotherapy as monotreatment and as compared to psychotherapy plus placebo. This advantage of the combined treatment was maintained while treatment was continued. Based on nine studies who conducted follow-up assessments, the advantage of the combined treatments disappeared after discontinuation of treatment. The combined treatment had a sustained advantage at follow-up over antidepressant therapy but no longer were there advantages over psychotherapy. Subgroup analyses revealed similar results for

studies focusing on PD patients with AG as compared to studies focusing on PD patients without AG.

1.5.7 Cost-effectiveness of PD treatments

PD carries considerable social and economic costs.[12,113-115] In the most recently published meta-analysis on PD however,[112] the authors note that none of the included studies reported on cost issues. Indeed, data evaluating costs associated with PD and the treatment of PD are scarce.[116] Further, drawing conclusions from the small number of studies is hampered by methodological differences between studies.[117] In current times, with limited health care resources, the question of cost-effectiveness is an important one.[118] Only a few studies however have not only evaluated treatment by their effectiveness but also looked into the cost-benefit ratio.[116,118-120]

Our special interest in light of the current thesis goes to studies comparing costs of CBT and medication treatment within a single design. One such study is the previously discussed multi-site randomized trial comparing imipramine, CBT, and their combination for PD.[101] In the economic evaluation of these data, monotreatments proved to be associated with greater cost-efficacy as compared to the combined treatment. After three months, imipramine was the most cost-efficacious treatment and six and nine months after treatment termination, this was the case for CBT.[116] It is important to note that only direct costs were assessed in this study. No studies on PD to date have examined the cost-effectiveness of direct and indirect costs (e.g., productivity loss) of the combined CBT+SSRI treatment compared to both monotherapies within a single design.

1.6 Summary empirical findings

Regarding CBT and SSRI as mono-treatments, evidence for short-term effectiveness is abundant. Long-term studies have been conducted less frequent. Regarding CBT, patients maintain high end state functioning in about half of the cases.[66] There is a need for studies investigating long-term effectiveness of CBT without concurrent medication. Regarding SSRI, patients generally remain panic free while on maintenance treatment but may relapse following medication taper. About one third of patients experienced a renewal of panic complaints after discontinuing medication within 28 weeks[97] but more studies are needed regarding this matter.

Two studies comparing both monotreatments found no superiority of CT over fluvoxamine[99] and paroxetine[100]. Note that in these studies, exposure was not a part of the CBT that was offered to patients. Investigations of SSRI use in the context of CBT and CBT use in the context of SSRI reveal that adding one modality to another may benefit patients previously not responding. For the present thesis, studies applying a combined SSRI and SSRI treatment are of particular interest. We are aware of six studies investigating the effectiveness of a combined pharmacotherapy and CBT treatment for PD and only two of those compared this combined treatment to both monotreatments. Overall, the combined treatment outperformed placebo and monotreatments on short term, up to twelve weeks[104,106-109] and as maintenance treatment.[101] Patients receiving pharmacotherapy were asked to taper medication in only two out of these six studies: in one study after 84 days[106], and in one study after nine months.[101] Both studies conducted a follow-up six months after treatment termination and found effects best preserved in treatment groups having received CBT. In the Sharp et al. study, patients in the combined treatment had needed the least additional treatment during follow-up. In the Barlow et al. study there was some evidence for a detrimental effect for the combined treatment being associated with a higher relapse rate as compared to the other groups. The other

studies listed in Table 1 report no post-treatment results except for the naturalistic follow-up study by De Beurs et al.[110] who found no loss of gains for the combined treatment group at follow-up.

In conclusion, more research on the effectiveness of the combined treatment both on short term but also with respect to maintaining treatment gains after medication taper, is needed.[56]

1.7 Discussion empirical findings

When comparing the different studies on the treatment of PD, some points deserve special consideration. First, drawing conclusions from different studies on CBT and/or SSRI is difficult due to methodological differences. Although recent meta-analyses apply sophisticated statistical techniques, the merits of different modalities (mono- and combined), will surface especially in studies investigating different treatment modalities within a single design.

Second, we would like to stress the importance of covering multiple areas of functioning when assessing treatment effectiveness. In some (efficacy) studies a reduction in panic attack frequency serves as the primary outcome measure thereby disregarding the multiple dimensions defining the morbidity of PD.[85]

Third, several authors stress the relevance of generalizability of findings by enhancing external validity. At this time, we would like to reflect on the issue of effectiveness versus efficacy. Once efficacy studies have shown a particular treatment to be efficacious under ideal conditions, effectiveness studies ask the question of what happens when this particular treatment is delivered in real-practice, under care as usual, and to a broad and representative group of patients.[121-123] When efficacy and effectiveness are seen as extremes on a dimensional scale, most studies described in this chapter are situated more on the efficacy than on the effectiveness side. Comparing CBT and/or SSRI in real-world

settings is considered an important endeavour which also enables evaluating treatments from an economic viewpoint.

In reviewing the existing literature on the treatment of PD, we conclude that there is a need for more data especially concerning the combined CBT+SSRI treatment. Questions awaiting further study include: Is the combined CBT+SSRI treatment more effective than either monotreatment? Is there a difference regarding different patient types e.g. patients with or without AG? What is the effect of tapering medication in patients receiving an SSRI? In summary, we observe the following points of consideration in designing future studies:

- There is a need for studies on psychological versus psychopharmacological treatments versus combined treatments within a single design.
- There is a need for long-term studies with additional treatment during follow-up well documented.
- There is a need for including patients both with (mild, moderate or severe) and without AG within a single design.
- In choosing outcome measures, there is a need for data covering multiple areas of functioning acknowledging the different aspects of PD morbidity.
- There is a need for more data on treatment gains after discontinuation of the SSRI.
- There is a need for studies on the effectiveness of PD treatments, e.g. data on 'real' patients receiving treatment under care as usual conditions and being treated in real-world settings.

To satisfy these needs, a randomized clinical trial was conducted in the Netherlands which will be introduced in chapter two.

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CHAPTER 2
INTRODUCTION PRESENT THESIS

TABLE OF CONTENTS

2.1 General introduction randomized controlled trial

A randomized clinical trial was conducted in the Netherlands comparing CBT, SSRI, and their combination aimed at treating PD with or without AG. The present thesis presents the results of this randomized clinical trial. Patients were treated for one year including medication taper and subsequently seen twice during the second (follow-up) year of the study. Tapering medication allowed us to investigate each modality's potential for maintaining results after treatment discontinuation. Our study is couched within current views on the importance of gathering data relevant for clinical practice. The overall goal of the study was to establish the best possible treatment for patients with PD with or without AG. This chapter presents overall methods, detailed information regarding applied treatments, and an overview of included studies and research goals. To conclude this introductory section, we will highlight some main characteristics of the present study:

- Three treatment modalities were investigated: CBT, SSRI, and CBT and SSRI combined.
- Duration treatment one year (including tapering medication).
- Duration study two years; two follow-ups in second year.
- Patients without or with mild, moderate, or severe AG were included.
- Data on costs were collected.
- Both academic and non-academic clinical sites participated.

2.2 Methods

This study was approved by the medical ethics committee of the University Medical Center in Groningen and subsequently by institutional review boards at each site. Patients were treated in eleven treatment facilities located throughout the Netherlands. Three kinds of sites participated: 1. university training and research centers (n = 2), 2. university research clinics (n = 2), and 3. regular mental health clinics (n = 7).

Sample size calculation was done beforehand and power analysis based on the Hamilton Anxiety Rating Scale (HAM-A),[1] also anticipating dropout, revealed that 152 patients had to be included. Regular patients seeking care at the participating treatment centers and meeting the study criteria were asked to participate in the study. Patients were also recruited through media advertisements and flyers which were distributed in general practitioner offices. Patients were enrolled between April 2001 and September 2003. Screening consisted of a structured interview, the M.I.N.I.[2] checking DSM-IV criteria for Axis I disorders.

Randomized patients suffered from a primary diagnosis of PD with or without AG. Inclusion was restricted to patients between 18 and 65 years of age. Patients who were pregnant, lactating, suicidal, psychotic, or severely depressed were ineligible to participate in the study. Further exclusion criteria comprised contraindications to either treatment or a concurrent competing treatment. Patients were not allowed to use psychotropic drugs except small doses of benzodiazepines (maximum the equivalent of 20 mg oxazepam per day). Patients were not required a predefined level of baseline severity (e.g. a minimum score on the HAM-A or a minimal number of panic attacks). The presence of comorbid Axis II disorders or Axis I disorders, other than severe depression or psychosis, was no reason for exclusion.

Written informed consent was obtained prior to randomization and after a full explanation of procedures. Randomization was stratified by site. For each site, an envelope containing a number of raffle tickets (CBT, SSRI, or CBT+SSRI) was present. The number of raffle tickets in the envelope was based on the number of patients the particular site expected to recruit. After drawing lots, the raffle tickets were not placed back in the envelope. When a patient met study criteria, local coordinators of the participating centers contacted a member of the research team who performed the drawing at the University Medical Center in Groningen by phone or e-mail. Beforehand, no information about the patient was interchanged.

After randomization, participating patients were assessed before starting treatment (pretest), after nine months of treatment (posttest 1), immediately after discontinuation of treatment (posttest 2), and six and twelve months after treatment discontinuation (follow-up 1 and follow-up 2). In between pretest and posttest 1, patients received 18 CBT and/or 9 SSRI sessions. In between posttest 1 and posttest 2, CBT patients received additional booster sessions resulting in up to 21 CBT sessions from pretest to posttest 2. SSRI patients tapered their medication during this period in which three additional sessions were scheduled resulting in up to 12 SSRI sessions from pretest to posttest 2.

Assessment consisted of completing a booklet with self-report questionnaires, and visiting a research assistant to be interviewed. Also, through-out the first treatment year patients were asked to register the frequency of panic attacks. Specific measurements (e.g. questionnaires) are introduced in further detail in subsequent chapters of the thesis.

All interviews for the study were conducted by carefully trained research assistants who were not involved in delivering the actual treatments and did not belong to the research team. These research assistants were not blind to treatment

allocation. In the two university training and research centers, CBT was delivered by master-level student-therapists who underwent extensive training and who were closely supervised during weekly gatherings. In the remaining treatment centers, CBT was performed by experienced clinical psychologists. All therapists received ongoing supervision on site. The SSRI treatment was delivered by experienced psychiatrists, psychiatrists in training or trained physicians.

Following each treatment session, all therapists completed a detailed form regarding the content of that session. These forms were evaluated by the research team in order to check treatment adherence. No physiological treatment checks (e.g. blood) were applied. The research team, situated at the University Medical Center in Groningen, was always available for any questions regarding the treatment(manual) or study design. Each of the three treatments was delivered in every treatment center. Before the start of the study, coworkers of all participating treatment centers assembled to discuss the treatment modalities and to integrate existing views. Because the study was designed to follow common practice in the treatment of PD, the treatment manuals were based on the outcomes of these gatherings to satisfy as closely as possible "care as usual" requirements. The manual-based treatments are introduced below.

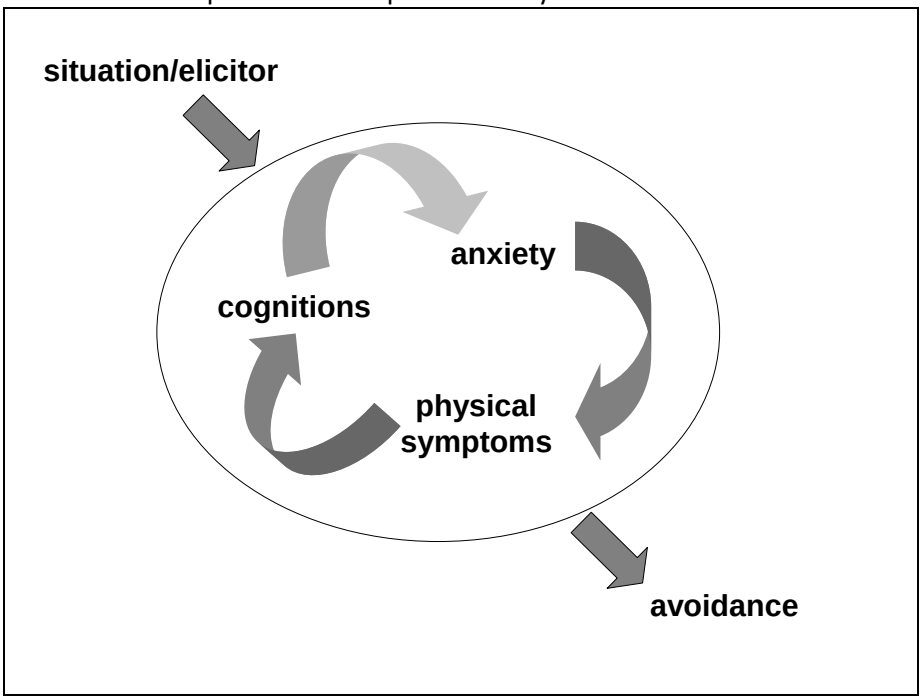
2.2.1 Cognitive behavioral therapy (CBT)

The CBT protocol was based on the work of Clark, Craske, and Barlow.[3-5] In order to prevent return of fear, sessions were expanded-spaced in the course of treatment (from once a week to twice a week, and from session 16 onward with 5 week intermissions).[6] During the first session, the patient received information about the

nature of the disorder and the treatment to be delivered. The treatment rationale was delivered based on the model depicted in Figure 2.1.

In the second session, interoceptive exposure was introduced and exercises were performed (throughout sessions 2 to 6) to provoke relevant bodily sensations which may resemble those symptoms experienced during a panic attack. By performing those exercises patients learn that bodily sensations can indeed be provoked, that these sensations spontaneously subside, and that these sensations[(7)] are not dangerous and are not followed by any harmful consequences.

Figure 2.1. CBT model of panic disorder as used in offering the treatment rationale to CBT patients in the present study



From session 6 onward, patients received cognitive therapy. During cognitive therapy, patients were first taught about the role of thoughts in generating emotions. Detailed discussion of emotions and associated cognitions led to the identification of specific beliefs, appraisals and assumptions. Patients were encouraged to examine the validity of their cognitions by considering all the available evidence and actively collecting new evidence. Both automatic appraisals (such as “if I panic, I will faint”) and core-level beliefs or schemata (such as “I am weak”) were examined in this manner. Based on this hypothesis testing, alternative cognitions were generated that were more evidence based and were experienced by patients as helping.

In the tenth session, exposure in vivo was introduced. When starting exposure in vivo, an individualized fear hierarchy was constructed. In between sessions, patients conducted self-guided exposure in vivo. Each exposure assignment was carefully designed and written down jointly by therapist and patient. Patients were instructed to stay in the feared situation until their anxiety level had dropped significantly. Safety-seeking behaviors were prohibited during the exposure exercises.

From session 10 onwards, both cognitive therapy and exposure in vivo were offered. The emphasis on one of both was left to the clinical judgment of the therapist. Homework assignments were given throughout the treatment and were thoroughly discussed at the beginning of each session. Each new treatment component was introduced with a separate treatment rationale. These rationales were handed-out to patients on paper so they could read them at home.

2.2.2 SSRI treatment

Patients randomized to receive pharmacological treatment either alone or in combination with CBT, received SSRI treatment for one year including medication taper. Patients receiving an SSRI visited their therapist 9 times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Each visit lasted approximately 20 minutes. SSRI prescriptions were in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association.[8] Pharmacotherapists could choose between 5 SSRIs currently prescribed in the Netherlands: fluvoxamine, fluoxetine, paroxetine, sertraline, and citalopram.

During the first SSRI session, patients received some general information on the role of serotonergic pathways in the brain involved in anxiety disorders and the working of SSRIs in panic disorder. Patients were administered a minimum dosage which was titrated upwards up to the effective range in the first month, and adjusted according to clinical response and tolerability. Pharmacotherapists were instructed to withhold from therapeutical interventions in order to avoid hidden exposure. Initiatives for exposing oneself to avoided situations were left to the patient.

2.2.3 Combined CBT+SSRI treatment

This treatment was administered according to the CBT and SSRI manuals. The two treatments started simultaneously and were delivered parallel. The CBT was delivered by the CBT therapist and the SSRI treatment was delivered by the pharmacotherapist.

2.3 Outline and aims of present thesis

The overall goal of the studies in the present thesis is to make a contribution to the on-going search for the best possible treatment for patients suffering from PD. To this end, we evaluated three empirically supported treatment modalities on short term, as maintenance treatment and post-treatment after discontinuation. Also, we aimed at testing the 'context-safety hypothesis' for which, based on outcome from treatment effectiveness studies, only limited evidence exists up to date. Additionally, the role of concurrent AG was investigated. Determining differential rate of improvement is also a goal of the present thesis. Finally, we evaluated treatment modalities economically e.g. determined their cost-effectiveness.

The present thesis starts with a general introduction. Chapters three through seven present the study results. To limit overlap between chapters, in the method sections of chapters three through seven only information regarding specific methods, relevant for the particular chapter, is presented. More general information on methods and design relevant for all studies presented in this thesis, are described only in the current chapter; chapter two.

In chapter three, treatment results after nine months are presented. The objective was to establish whether CBT+SSRI was more effective than either CBT- or SSRI-only after nine months of treatment before medication taper, and to evaluate any differential effects between the monotreatments.

In chapter four, long-term results are presented. The three treatment modalities were compared up to the second follow-up, twelve months after treatment discontinuation, in order to examine the differential long-term effectiveness of the three treatment modalities with the ultimate goal of determining the most effective treatment for PD with or without AG. Also in this

chapter, the relationship between treatment outcome and seven predictor variables was investigated. These variables included treatment site, baseline agoraphobia, duration of illness, Axis I en Axis II comorbidity, additional benzodiazepine use, and additional treatment during follow-up.

Next to pre-post outcome measures we also collected more continuous data. In order to establish possible differences regarding rate of improvement, frequency of panic attacks was assessed through-out the whole year of active treatment and subsequently analyzed. The results of these analyses are presented in chapter five. Research goals were to examine the rate of improvement in panic attack frequency during treatment and to establish possible differential effects in rate of improvement across treatment modalities. Also, the effect of tapering medication across treatment modalities was examined. Finally, the relationship between rate of improvement in panic frequency and baseline severity of agoraphobia was examined.

Chapter six presents the economic evaluation of the three treatment modalities. The following research question was addressed: Which intervention, CBT, SSRI, or CBT+SSRI is most cost-effective in the treatment of patients with PD with or without AG?

Finally, in chapter seven, overall results of the presented studies are discussed. Limitations are presented and suggestions for further research are provided.

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CHAPTER 3

TREATMENT RESULTS AFTER NINE MONTHS; BEFORE MEDICATION TAPER

This chapter is a slightly altered version of a previous publication:
Is a combined therapy more effective than either CBT or SSR alone? Results of a multicenter trial on panic disorder with or without agoraphobia.
Franske J. van Apeldoorn, Wiljo J.P.J. van Hout, Peter Paul A. Mersch, Mark Huisman, Bernhard R.Slaap, William W. Hale III, Sako Visser, Richard van Dyck, Johan A. den Boer (2008).
Acta Psychiatrica Scandinavica; 117(4): 260-270.

ABSTRACT

The objective of the present study was to establish whether the combination of CBT with SSRI was more effective in treating PD than either CBT or SSRI alone, and to evaluate any differential effects between the monotreatments. PD patients (n = 150) with or without AG received CBT, SSRI, or CBT+SSRI. Outcome was assessed after nine months, before medication taper. CBT+SSRI proved clearly superior to CBT in both completer and ITT analysis. Completer analysis revealed superiority of CBT+SSRI over SSRI on three measures and no differences between CBT and SSRI. ITT analysis revealed superiority of SSRI over CBT on four measures and no differences between CBT+SSRI and SSRI. It was concluded that both the monotreatments (CBT, SSRI) and the combined treatment (CBT+SSRI) proved to be effective treatments for PD. At posttest, CBT+SSRI was clearly superior to CBT but differences between CBT+SSRI and SSRI, and between SSRI and CBT, were small.

INTRODUCTION

The life-time prevalence rate for PD without AG is estimated at 3.7%, and for PD with AG at 1.1%. [1] In clinical samples, the majority of the PD patients also suffer from AG. There is a wealth of data supporting the efficacy of both Cognitive-Behavioral Therapy (CBT) and pharmacotherapy using Serotonin Selective Reuptake Inhibitors (SSRI) in the treatment of PD.[2-5]

The successes of both pharmacotherapy and psychological treatments have led to the hope that the combination of these modalities might further increase efficacy. The added value of a combined treatment may stem from an attenuating effect of the medication on anxiety which in turn might facilitate the exposure component in CBT.[6] It is suggested however, that this attenuating effect lasts only as long as medication is continued.[7] If this is true, the superiority of the combined treatment is most evident when treatment effect is assessed before medication taper.

Several studies investigated the efficacy of the combination of antidepressants with CBT.[8-17] However, only two studies compared both monotreatments (CBT-only and antidepressants-only) with a combination of both.[8;16]

Sharp et al.[16] compared five treatments: CBT + fluvoxamine, fluvoxamine, CBT, CBT + placebo, and placebo (n = 190). After twelve weeks, before medication taper, the combination of CBT + fluvoxamine was found to be equally effective as the other active treatments. A similar design was employed in the study by Barlow et al.[8] Patients (n = 312) were randomly assigned to receive CBT + imipramine, imipramine, CBT, CBT + placebo, and placebo. After nine months, before medication taper, the combination of CBT and imipramine was superior to all other treatments on one out of two main outcome measures, a clinician rated scale of PD severity.

To our knowledge, head-to-head comparisons between CBT and antidepressants were made in five studies.[8;16;18-20] Before medication taper, Clark et al.[20] found imipramine and Cognitive Therapy (CT) to be equally effective, while Baker et al.[18] and Black et al.[19] both found an SSRI treatment to be superior to CT.

In the Barlow et al. and Sharp et al. studies,[8;16] no significant differences were detected between CBT-only and pharmacotherapy-only.

In sum, some evidence favoring the combined treatment over monotreatments at treatment endpoint was established by one study with imipramine,[8] while no add-on effect of the combined treatment was found by another study with fluvoxamine.[16] Further, studies show either no differences between CBT and pharmacotherapy, or results favor the SSRI treatment.

When reviewing the data, two related issues must be taken into account. First, the delivered CBT-ingredients differ substantially which makes it difficult to compare overall results. Although consensus has not been reached regarding which CBT components are essential and which components might be redundant in the treatment of PD with and PD without AG, (in vivo) exposure is generally considered to be superior to CT in treating AG.[21] In both studies that yielded results favoring SSRI over CT, exposure techniques were not applied notwithstanding the fact that moderate to severe agoraphobics participated in these studies.[18;19] Second, although all studies included patients with PD, they differed on the inclusion of agoraphobics. For instance, Barlow et al.[8] included only patients with no or mild AG. Accordingly, methodological differences among studies preclude drawing unambiguous conclusions on outcome.

As a contribution to the quest for the best possible treatment for patients suffering from PD with or without AG the present study evaluated three treatments: CBT, SSRI, and the combination of both (CBT+SSRI). Because previous efficacy studies have established the superiority of the treatments under scrutiny over placebo,[3;4] a placebo group was not included. Our goal was to establish the effectiveness of treatment for PD in daily clinical practice and to ensure external validity, treatments were delivered at both research and non-research sites, within a naturalistic context. It was expected that any benefits of the combined treatment would be most obvious before medication taper. Therefore, in line with the Barlow et al. study,[8] posttest was scheduled after nine months of treatment so that patients had ample time to

benefit from treatment. Medication taper started after posttest was conducted. The objective was to establish whether CBT+SSRI was indeed more effective than either CBT- or SSRI-alone, and to evaluate any differential effects between the monotreatments.

METHOD

Randomized patients suffered from a primary diagnosis of PD with or without AG. Once included, AG level was assessed by the first author based on chart review and the structured interview. Patients were classified as not suffering from AG, or suffering from mild, moderate or severe AG following guidelines set forth by the DSM-III-R. Patients received CBT, SSRI, or CBT+SSRI. Posttest was completed after nine months before medication taper; i.e. after 18 CBT sessions and/or 9 SSRI sessions. Patients in the CBT group received up to 18 CBT sessions each lasting approximately 50 minutes. Patients receiving an SSRI visited their therapist 9 times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Each visit lasted approximately 20 minutes. In the combined treatment CBT and SSRI started simultaneously and were delivered parallel. The CBT was delivered by the CBT therapist and the SSRI treatment was delivered by the pharmacotherapist.

Assessment

In the present study we will report on six outcome measures: four continuous measures (regarding avoidance, anxiety, depression, and general psychopathology) and two categorical measures (responder status and panic free status).

Patients were defined panic free when they reported no panic attacks in a panic-log during a two week period after nine months of treatment (posttest). Also at posttest, PD severity and degree of improvement were evaluated by both the

patient and an independent rater using the Patient Global Evaluation (PGE), and the Clinical Global Improvement scale (CGI) respectively.[27] On the improvement scales, a score of 1, 2 or 3 (very much improved to improved) was needed to meet responder criteria. On the severity scales, a score of 1 or 2 (no complaints or only mild complaints) was needed. Patients were classified as responders when they met these criteria for at least three out of four PGE/CGI scales (PGE Improvement, PGE Severity, CGI Improvement, and CGI Severity).

The Hamilton Anxiety Rating Scale (HAM-A)[28] and the Hamilton Depression Rating Scale (HAM-D)[29] were administered by trained research assistants. Two self-report questionnaires yielded information regarding agoraphobic avoidance (the 5-item Agoraphobia subscale of the Fear Questionnaire (FQ-AG),[30] and regarding general psychopathology (the total score on the Symptoms Checklist (SCL-90).[31;32]

Statistical Analyses

Pretest differences between randomized groups were analyzed by univariate analyses of variance (ANOVAs) or nonparametric equivalents if called for. Chi-square analyses, Fisher Exact tests, and analysis of covariance were used to detect possible site differences. Time effects per treatment were analyzed with t-tests for dependent samples. Differential treatment effects were analyzed twice; for the completer (n = 100) and the intent-to-treat (ITT; n = 145) samples. In the ITT analysis, pretest scores for dropout patients were carried forward to posttest as an assumption of non-response or return to pretest level. Note that because no pretest scores for responder status were present, only completer results are available for this particular outcome measure.

Chi-square analyses were used to investigate overall differences in responder- and panic-free rates. Pair-wise differences between proportions were evaluated by the Wilson 95% confidence interval (CI) around this difference.[33] Analyses of covariance (ANCOVAs), using the pretest score as covariate, were used for all

continuous measures. Contrasts (non-orthogonal) were computed to evaluate pair wise differences among the adjusted means. For the multiple comparisons, alpha levels were corrected according to the Bonferroni-Holm procedure.[34] When CBT+SSRI was compared to either monotreatment, the one-tailed *P*-value was used. Post hoc effect sizes (indexed by Pearson's correlation coefficient $r = \sqrt{t^2/t^2 + df}$ which ranges from 0 to 1) were calculated for both the within-group pre- to posttest changes and all between-group comparisons. According to suggestions made by Cohen,[35], an effect size of ± .10 constitutes a small effect, an effect size of ± .30 constitutes a medium effect, and an effect size of ± .50 constitutes a large effect.

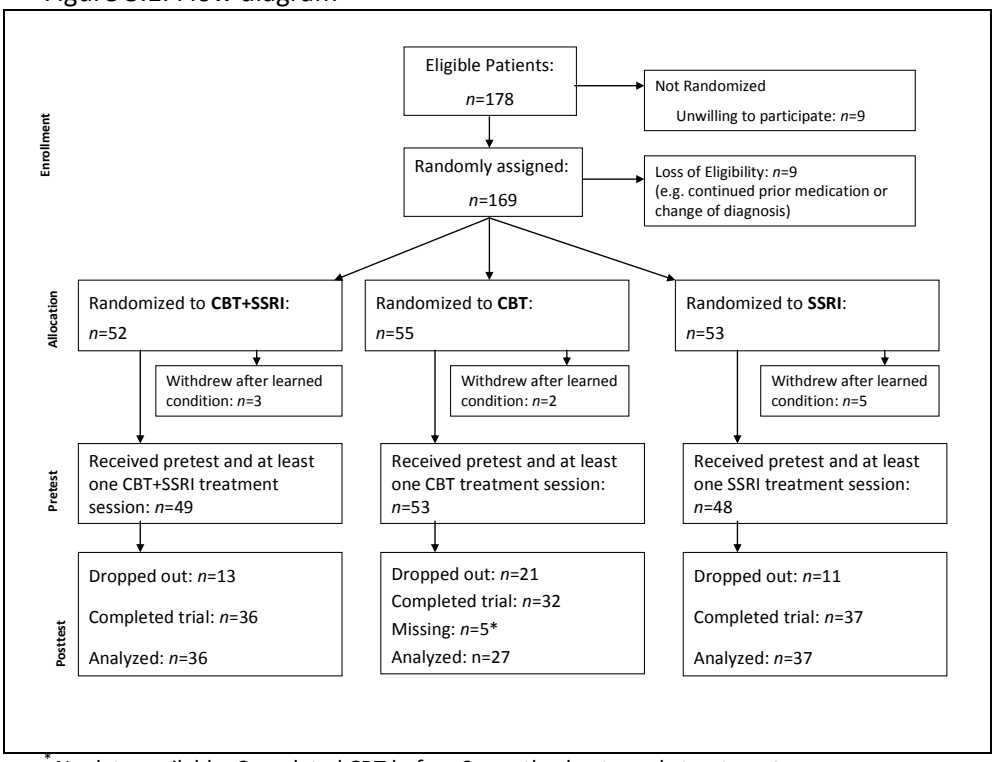
Unless stated differently, tests were two-tailed and alpha was set at .05.

RESULTS

Intake summary and pretest analyses

One hundred and seventy-eight eligible patients were seen for screening (see Figure 3.1). Subsequently, 150 patients started with CBT+SSRI (n = 49), CBT (n = 53), or SSRI (n = 48). In total, 54.7% of the sample was female (see Table 3.1). Mean age was 37.5 years (range 18-61 years).

Figure 3.1. Flow diagram



* No data available: Completed CBT before 9 months due to early treatment success.

Sixty-three patients were treated at the two university training and research centers, 42 at the two university research clinics, and 45 patients at the seven regular mental health clinics.

When analyzing pretest scores, a significant difference was detected on the CGI (F=5.7; df=2 ; P = 0.004) indicating that patients treated at the university research clinics had somewhat higher pretest CGI scores than patients treated at the other sites. Also, the level of completed education was lower for patients treated at non-research sites as when compared to patients treated at research sites (χ^2 = 8.8 ; df = 3 ; P = 0.03). No other significant site differences were detected at baseline (all $P \geq$ 0.22).

The classification of AG types (no, mild, moderate, severe) was supported by pretest scores on the FQ-AG. The following means were found: no AG: mean FQ-AG 6.3 (SD 6.3), mild AG: mean FQ-AG 13.3 (SD 9.1), moderate AG: mean FQ-AG 22.4

(SD 10.4), and severe AG: mean FQ-AG 31.1 (SD 8.0) ($F = 29.1$; $df = 3$; $P < 0.001$). About half of the patients (48%) had no or mild AG whereas 52% suffered from moderate or severe AG.

At pretest, patients with moderate or severe AG obtained significant higher means (scored more severe) than patients without or with mild AG on each outcome measure (all $P \leq 0.05$).

Patients in the CBT+SSRI group were slightly younger than in the other treatment groups ($F=3.23$; $df=2$; $P = 0.04$) with mean age ranging from 34.4 (CBT+SSRI) to 39.4 (CBT). No other significant differences regarding patient characteristics among the three randomized treatment groups were found (all $P \geq 0.18$). Also, analyses performed on each outcome measure yielded no significant differences between treatment groups at pretest (all $P \geq 0.27$).

Table 3.1. Pretest characteristics for three patient groups

Pretest Characteristic	CBT (n=53)		SSRI (n=48)		CBT+SSRI (n=49)		All Patients (n=150)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Duration of illness*	8.1	8.4	10.2	10.4	7.2	7.6	8.5	8.9
Age	39.4	10.2	38.5	10.5	34.4	10.6	37.5	10.6
Nr of Panic attacks**	5.44	9.57	3.62	4.50	5.08	5.75	4.74	6.99
PGE, severity	3.45	1.08	3.53	1.06	3.51	1.12	3.47	1.07
CGI, severity	2.94	1.00	2.90	.84	2.76	.94	2.89	.95
FQ-subscale AG	18.08	11.94	17.32	12.21	20.94	10.70	18.78	11.66
HAM-A	25.46	10.65	21.94	9.78	23.29	8.54	23.62	9.77
HAM-D	15.21	7.30	14.23	7.47	14.61	6.51	14.70	7.07
SCL-90	196.21	55.66	186.24	65.10	192.99	49.83	192.01	56.82
	n	%	n	%	n	%	n	%
Female sex	33	62.3	26	54.2	23	46.9	82	54.7
Currently married***	29	54.7	33	68.8	25	51.0	87	58.0
Currently employed	30	56.6	31	64.6	31	63.3	92	61.3
Level of completed education :								
low	10	18.9	11	24.4	11	22.4	32	21.8
moderate	28	52.8	16	35.6	14	28.6	58	39.5
above moderate	6	11.3	9	20.0	9	18.4	24	16.3
high	9	17.0	9	20.0	15	30.6	33	22.4
AG level:								
no or mild	26	49.1	23	47.9	23	46.9	72	48.0
moderate or severe	27	50.9	25	52.1	26	53.1	78	52.0
Benzodiazepine users****	18	34	12	25	14	28.6	44	29.3
Having received previous CBT treatment	2	3.8	3	6.4	7	14.3	12	8.1
Having received previous SSRI treatment	17	32.1	12	25.0	14	28.6	43	28.7
Comorbid Axis I disorder present	28	52.8	20	41.7	20	55.1	75	50.0

Notes: * in years ** mean number of panic attacks during two-week pretest period. *** or cohabiting with steady partner. ****benzodiazepine use could vary between very infrequent use to daily use. PGE = Patient Global Evaluation, CGI = Clinical Global Impression, FQ = Fear Questionnaire, HAM-A = Hamilton Anxiety Rating Scale, HAM-D= Hamilton Depression Rating Scale, SCL-90 = Symptoms Checklist.

Attrition

A total of 45 patients (30% of 150 patients who had started treatment) dropped out of treatment. There was no significant difference in patient dropout rate between treatment groups although more patients dropped out of CBT (39.6%: n = 21) as compared to CBT+SSRI (26.5%: n = 13) and SSRI (22.9%: n = 11) (χ^2 = 3.76; df = 2; *P* = 0.15). As compared to completers, significantly more patients who subsequently dropped out had previously used an SSRI (*P* = 0.02, Fisher's exact test). No other significant differences between completers and dropouts on outcome variables or regarding patient characteristics at pretest were found (all *P* ≥ 0.07).

Reasons for dropout included side effects of medication (n = 11 (24.4%), including 4 CBT+SSRI and 7 SSRI patients), life events not related to treatment (n = 3 (6.7%), all 3 CBT patients), non-compliance (n = 10 (22.2 %), including 4 CBT+SSRI, 5 CBT, and 1 SSRI patients), needing other treatment (n = 6 (13.3%), including 3 CBT+SSRI, 2 CBT, and 1 SSRI patients), loosing motivation because of good results (n = 1 (2.2 %), CBT patient), not satisfied with obtained results (n = 5 (11.1%), including 1 CBT+SSRI and 4 CBT patients), using medication outside protocol (n=3 (6.7%), all 3 CBT patients), and unknown reasons (n = 6 (13.3%), including 1 CBT+SSRI, 3 CBT, and 2 SSRI patients).

Site differences

To detect possible site differences, several analyses were performed. First, dropout rates were compared between the three types of sites (site clusters 1 to 3, see chapter 2) and between research and non-research sites (site clusters 1+2 compared to 3) and no significant differences were found (*P*-values 0.92 and 0.85 respectively). Second, possible differences in treatment effect between sites were analyzed and no significant differences were found (all *P* ≥ 0.09). Finally, analyses were repeated for only the patients who had received CBT because possible site differences were

believed to have the greatest impact on this group of patients. Next to comparing the three sites and comparing research and non-research sites, we also checked for differences between sites using student therapists (site cluster 1) and sites not using student therapists (site clusters 2 and 3) to see whether therapist level of experience was a factor of importance. For CBT patients, site differences were thus analyzed in three ways and taken these analyses together, no differences in dropout rate (all $P \geq 0.95$) or treatment outcome (all $P \geq 0.09$) were detected.

Treatment effects

Table 3.2 shows the adjusted posttest scores, confidence intervals, and effect sizes for the continuous outcome measures. The posttest proportions of panic free patients and responders are depicted in Figures 3.2 and 3.3 respectively. Mean within-group effect sizes are presented in Table 3.3.

Because patients in the CBT+SSRI group were slightly younger than in the other treatment groups, the effect of age on treatment effect was investigated using covariance analysis. No main effect of age was found on any measure (all $P \geq 0.11$).

All patients, regardless of received treatment, showed significant improvements from pre- to posttest on all outcome measures, both in the completer and the ITT analysis (all $P \leq 0.01$). For the sake of brevity, we will only report the pair wise comparisons. Regarding the ITT analysis, only the differences between the completer and the ITT analysis will be highlighted.

CBT+SSRI versus CBT : Completer analysis revealed that CBT+SSRI was superior to CBT on the FQ-AG ($F = 9.87$; $df = 1$; $P = 0.001$), HAM-A ($F = 9.17$; $df = 1$; $P = 0.002$), SCL-90 ($F = 14.0$; $df=1$; $P < 0.001$), HAM-D ($F = 13.3$; $df = 1$; $P < 0.001$), and regarding the proportion of patients reaching panic free status (95% CI of difference in proportion from .17 to .58). Significance was not reached regarding the proportion of patients reaching responder status (95% CI of difference in proportion from - .36

to .13). In the ITT analysis, the hypothesized superiority of CBT+SSRI to CBT was confirmed on all outcome measures (all $P \leq 0.002$, and for proportion panic free status 95% CI of difference in proportion from .20 to .56).

CBT+SSRI versus SSRI: Completer analysis favored CBT+SSRI over SSRI on the HAM-D ($F = 5.1$; df=1; $P = 0.01$), SCL-90 ($F = 3.0$; df = 1; $P = 0.04$), and regarding the proportion of patients reaching panic free status (95% CI of difference in proportion from .08 to .43). Significance was not reached regarding the proportion of patients reaching responder status (95% CI of difference in proportion from -.28 to .08), not on the HAM-A ($F = 1.9$; df = 1; $P = 0.08$), and also not on the FQ-AG ($F = 2.7$; df = 1; $P = 0.05$). In the ITT analysis, no significant differences between CBT+SSRI and SSRI were observed on any measure.

CBT versus SSRI: Completer analysis showed no significant differences between SSRI and CBT on any measure (all $P \geq 0.03$). In the ITT analysis, SSRI was superior to CBT on the HAM-A ($F = 6.5$; df = 1 ; $P = 0.01$), HAM-D ($F = 5.1$; df = 1 ; $P = 0.02$), SCL-90 ($F = 7.0$; df = 1 ; $P = 0.01$), and regarding the proportion of patients reaching panic free status (95% CI of difference in proportion from .02 to .41).

Table 3.2. Adjusted posttest scores and confidence Intervals on four continuous outcome measures, and within- and between group effect sizes for both completer and intent-to-treat samples

Measure	Treatment modality	Adjusted mean posttest	95% Confidence Interval	*r* within	*r* within	*r* C+S vs. C	*r* C+S vs. S	*r* C vs. S	*r* C+S vs. C	*r* C+S vs. S	*r* C vs. S
		com	com	com	ITT	com	com	com	ITT	ITT	ITT
FQ-subscale AG (0-40)	CBT	10.83	7.89 to 13.77	.62	.45						
	SSRI	7.69	5.20 to 10.19	.78	.68	.31	.17	.17	.24	.08	.16
	CBT+SSRI	4.76	2.28 to 7.24	.85	.72						
HAM-A (0-56)	CBT	16.01	12.52 to 19.49	.69	.49						
	SSRI	11.89	9.08 to 14.70	.76	.66	.30	.14	.19	.27	.07	.21
	CBT+SSRI	9.11	6.24 to 11.97	.87	.73						
HAM-D (0-52)	CBT	11.17	8.79 to 13.55	.51	.37						
	SSRI	8.61	6.68 to 10.54	.70	.62	.36	.23	.17	.36	.23	.17
	CBT+SSRI	5.50	3.54 to 7.46	.79	.68						
SCL-90 (90-450)	CBT	157.79	143.99 to 171.58	.58	.42						
	SSRI	138.23	126.58 to 149.88	.73	.64	.37	.18	.22	.31	.09	.22
	CBT+SSRI	123.77	112.13 to 135.42	.83	.71						
			Mean between-group effect sizes:			.34	.18	.19	.30	.12	.19

Notes: Posttest means are adjusted to pretest levels. CBT: n pretest=53, n posttest=27, SSRI: n pretest=48, n posttest=37, CBT+SSRI: n pretest=49, n posttest=36. FQ= Fear Questionnaire, HAM-A = Hamilton Anxiety Rating Scale, HAM-D = Hamilton Depression Rating Scale, SCL-90 = Symptoms Checklist. r= effect size: ranging from 0 to 1. com = completer analysis, ITT= intent-to-treat analysis. Between group effect sizes r: C = CBT, S = SSRI, C+S= combined CBT+SSRI.

In sum, CBT+SSRI was superior to CBT on five outcome measures in both completer and ITT analysis. CBT+SSRI was superior to SSRI on three measures in the completer analysis but not on any measure in the ITT analysis. SSRI did not outperform CBT in the completer analysis but proved superior to CBT on four measures in the ITT analysis. Thus, compared to the completer analysis, CBT performed poorer whereas SSRI performed better in the ITT analysis.

Figure 3.2. Proportions of panic free patients at posttest for both completer and intent-to-treat samples

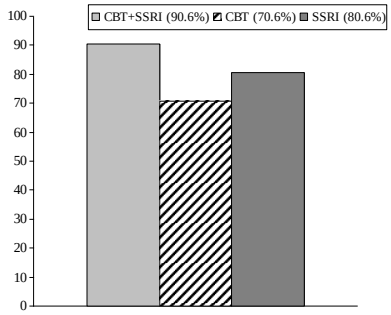


Figure 3.3. Proportions of patients meeting responder criteria at posttest for the completer sample

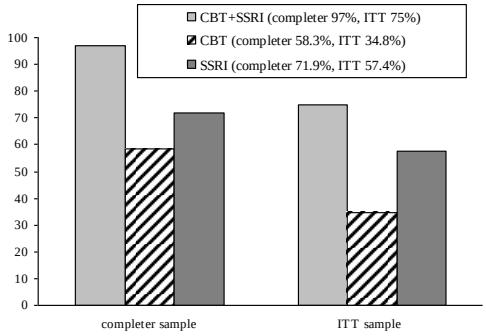


Table 3.3. Within-group effect sizes for CBT-only, antidepressant-only, and the combination of both, for six studies

	present study[a]	Barlow et al. 2000[b]	Sharp et al. 1996[c]	Clark et al. 1994[d]	Bakker et al. 1999[e]	Black et al. 1993[f]
Completer:						
CBT-only	.60	.62	.71	.64	.44	.37
antidepressant-only	.74	.72	.51	.53	.67 par., .54 clom.	.63
combined therapy	.84	.80	.69	/	/	/
Intent-to-treat:						
CBT-only	.43	.41	/	/	.29	.35
antidepressant-only	.65	.45	/	/	.58 par. , .51 clom.	.43
combined therapy	.71	.59	/	/	/	/

a: Mean effect sizes based on effect sizes in Table 3.2. CBT: interoceptive exposure, cognitive therapy, and exposure in vivo. Antidepressants: fluoxetine, fluvoxamine, citalopram, sertraline, or paroxetine.

b: Based on the means and SDs presented in Tables 1 and 2 (8), *d* was computed for one outcome measure. Subsequently *d* was converted into *r*. CBT: interoceptive exposure, cognitive restructuring, and breathing retraining. Antidepressant: imipramine.

c: Based on the means and SDs kindly provided to us by Dr Sharp, Cohen's *d* was computed for three outcome measures. The mean *d* was subsequently converted into *r*. CBT: cognitive and behavioral panic management techniques including exposure. Antidepressant: fluvoxamine (16). ITT analysis was not performed.

d: Based on the means and SDs presented in Table 2 (20), Cohen's *d* was computed for 19 outcome measures. The mean *d* was subsequently converted into *r*. CBT: cognitive therapy. Antidepressant: imipramine. ITT analysis was not performed.

e: Based on the effect sizes in Table 3 (18), a mean *d* was computed, subsequently *d* was converted into *r*. CBT: cognitive therapy. Antidepressants: par.=paroxetine, clom.=clomipramine.

f: Based on the means and SDs presented in Table 2 (19), Cohen's *d* was computed for six outcome measures. The mean *d* was subsequently converted into *r*. CBT: cognitive therapy. Antidepressant: fluvoxamine.

DISCUSSION

The present findings corroborate the predicted superiority of CBT+SSRI over CBT. This superiority was demonstrated on all outcome measures in the completer analysis except the categorical outcome measure responder status. The predicted superiority of CBT+SSRI over SSRI was not confirmed. Although the mean posttest scores were consistently lower for CBT+SSRI as compared to SSRI, significance was reached for only three out of six measures in the completer and no measures in the ITT analysis suggesting that the added value of CBT to SSRI-only is limited. The small mean between-group effect sizes (ES) (both completer and ITT) for CBT+SSRI versus SSRI point in the same direction. Note that, to our knowledge, this is the first study on PD to report between-group ES which probably offer the most insight into the magnitude of observed differences between groups.

In the Barlow et al. and Sharp et al. studies,[8;16] no significant differences between CBT-only and antidepressant-only emerged. Completer analysis revealed no significant differences between the monotreatments but SSRI was superior to CBT on four measures in the ITT analysis. This might raise questions regarding the CBT treatment as delivered in the present study. In order to be able to compare the present results to previous findings, (mean) within group ES were computed for relevant studies (see Table 3.3). In general, substantial differences between completer and ITT ES are observed. This might be explained by diverging attrition rates since an uneven distribution in dropouts between treatments may favor one treatment over another in the ITT analysis. For example, in the present study the dropout rates for respectively the combined treatment, antidepressant-only treatment, and CBT are 26.5%, 22.9%, and 39.6% compared to 38.8%, 62.7% and 37.5% which we derived from the Barlow et al. study.[8] While in the present study the highest dropout rate was observed for CBT-only, in the Barlow et al. study, the highest dropout rate was observed for the anti-depressant only treatment. This explains why, in the latter study, the greatest change between completer and ITT ES

was observed for the antidepressant-only treatment, while in the present study the greatest change between completer and ITT ES was observed for the CBT-treatment. Based on the observed ES (CBT present study 0.60 completer, 0.43 ITT, CBT Barlow et al. 0.62 completer, 0.41 ITT) and dropout rates (present CBT dropout rate 39.6%, CBT dropout rate in the Barlow et al. study 37.5%,), it seems safe to conclude that CBT in the present study did not perform worse compared to previous studies but that the delivered CBT+SSRI and SSRI treatments simply performed better. Please note that the high antidepressant dropout rate in the Barlow et al. study (62.7% compared to 22.9% in the present study) might be explained by the use of imipramine instead of an SSRI. SSRIs are known for their greater tolerability in comparison to tricyclic antidepressants such as imipramine.[36]

Patients with different AG severity levels participated in the present study. At pretest, patients with moderate or severe AG obtained significant higher means (scored more severe) than patients without or with mild AG on each outcome measure. Post-hoc, univariate analyses of variance was applied again but this time on the posttest scores. By that time, except for the FQ-AG, differences between both AG groups were no longer significant. This might suggest that patients with moderate or severe AG, although still reporting more agoraphobic behavior at posttest, benefit as much from treatment as patients without or with only mild AG. Clearly, the relationship between AG level and treatment outcome warrants further investigation.

Strengths of the present study include the fact that both academic and non-academic clinical sites participated. Results show that CBT, SSRI, and CBT+SSRI are effective treatments in clinical practice. No site differences were detected and patients improved equally well regardless of whether they were treated at research or non-research sites. Criteria for patient selection were liberal, and treatments were delivered according to care as usual. Therefore, the present findings can be considered highly externally valid with respect to type of patients, type of treatments, and type of treatment centers.

Establishing the effectiveness of treatment for PD in daily clinical practice was set as the main goal. Therefore, in ensuring external validity, some decisions were made which might have affected internal validity. First, although therapists completed a detailed form regarding session content following each treatment session, more formal treatment integrity or treatment fidelity checks (such as audio taping each session or screening blood or urine samples) were not applied because this was found to be logistically impractical and also incompatible with our intention to simulate clinical practice.

Second, patients were allowed comorbid use of benzodiazepines and the effects of benzodiazepines and the SSRIs might thus be intertwined. It is however unlikely that the present findings can be accounted for by additional benzodiazepine use since pretest benzodiazepine use was evenly distributed across treatments and can therefore not account for the observed posttest differences in outcome. Also, Otto et al.[37] found no significant difference in the effect size outcome between studies that prohibited and studies that allowed concurrent medication use.

Third, Sharp et al.[16] note that a problem of most comparative studies is the lack of control for therapist contact. The present study too suffers from this alleged problem because patients receiving CBT spent more time with their CBT therapist as compared to the time that patients receiving SSRI spent with their pharmacotherapist. However, contact time is a characteristic inherent to the different treatment modalities and correcting this 'problem' would have severely limited the generalizability of our results.

In summary, the present study demonstrated that, consistent with previous findings reported by Barlow et al.,[8] a combined treatment is superior to monotreatment although the difference between SSRI-only and the combined treatment was only modest. Also, this multicenter study supports the transportability of CBT, SSRI, and CBT+SSRI from research to non-research settings. Finally, patients with moderate or severe AG were not excluded and results are thus generalizable to the whole AG continuum.

Probably the most urgent matter raised by present findings is the question of maintenance of treatment gains. The risk of relapse after tapering medication is considerable as is demonstrated in different studies in which only pharmacotherapy was studied.[38] One may reason that adding CBT to the pharmacotherapy might prevent relapse. However, there are also indications that the combined treatment does not prevent relapse but even encourages it.[8;39] Thus although present findings suggest that the combined treatment has a greater effectiveness after nine months of treatment as compared to CBT-only and, to a lesser extent, SSRI-only, the true challenge for the combined treatment may be still ahead, when the SSRIs are tapered off.

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CHAPTER 4

TREATMENT RESULTS UNTIL ONE YEAR FOLLOW-UP

This chapter is a slightly altered version of a previous publication:
CBT or SSRI or both combined for panic disorder with or without agoraphobia: Treatment results until one year follow-up.
Franske J. van Apeldoorn, Marieke E. Timmerman, Peter Paul A. Mersch, Wiljo J.P.J. van Hout, Sako Visser, Richard van Dyck, Johan A. den Boer (2010).
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ABSTRACT

The main objective of the present study was to establish the long-term effectiveness of three treatments for PD with or without AG: CBT, SSRI, and CBT+SSRI. As a secondary objective, the relationship between treatment outcome and seven predictor variables was investigated. Patients were randomized to treatment. Academic and non-academic clinical sites participated. Each treatment modality lasted one year. Pharmacotherapists were free to choose between five SSRIs currently marketed in the Netherlands. Outcome was assessed after nine months of treatment (posttest 1), after discontinuation of treatment (posttest 2), and six and twelve months after treatment discontinuation (follow-up 1 and follow-up 2). About half of the patients did not suffer from AG or suffered from only mild AG (48.7%), while the other half suffered from moderate or severe AG (51.3%). Patients in each treatment group improved significantly from pre- to posttest 1 on the primary outcome measures level of anxiety, degree of coping, and remitter status, as well as on the secondary outcome measures depressive symptomatology, health related quality of life, and treatment satisfaction. Gains were preserved from posttest 2 through-out the follow-up period. Some superiority of CBT+SSRI and SSRI as compared to CBT was observed at posttest 1. However, at both follow-ups, differences between treatment modalities proved non-significant. Thus, no fall-off in gains was observed for either treatment modality after treatment discontinuation. Gains produced by CBT were slower to emerge than those produced by CBT+SSRI and SSRI but CBT ended sooner and was not associated with adverse effects.

INTRODUCTION

Panic disorder (PD) is associated with substantial reduction in quality of life[1] and carries considerable social and economic costs.[2;3] Additionally, PD typically runs a chronic course and relapse rates are high.[4] The question of maintenance of gains post-treatment is therefore of considerable clinical relevance.

PD can be treated with both psychological and psychopharmacological interventions. Serotonin Selective Reuptake Inhibitors (SSRIs) are recommended as first choice treatment within the pharmacotherapeutical armamentarium.[5;6] Cognitive-Behavioral Therapy (CBT) is considered to be the most effective psychological treatment for PD.[7;8] In clinical practice, patients with PD often receive a combination of these interventions and these combination treatments have increasingly received attention within the field.

In a review[9] of 23 studies it was concluded that combined treatments were superior to antidepressants in all phases monitored, that is in the acute treatment phase, during continuation treatment and also after termination of treatment. Combined treatments were also superior to psychotherapy in the acute treatment phase and during continuation treatment. In contrast, after termination of treatment (follow-ups ranging from 6 to 24 months), the combined treatments and psychotherapy proved to be equally effective. Not all studies included in this review allowed a direct comparison between CBT-only, antidepressant-only and the combination of both.

In a study that did employ all three treatment modalities, Barlow et al.[10] randomized 312 patients to receive CBT, placebo, imipramine, CBT+imipramine, or CBT+placebo. Treatment lasted nine months (12 weeks of acute treatment followed by a six-month treatment continuation phase followed by the tapering of medication). Patients were re-assessed six months after treatment discontinuation. Results indicated that patients in the imipramine and CBT+imipramine groups had received the most additional treatment during the follow-up period. Also,

CBT+imipramine was associated with the highest relapse rate. At follow-up, the only groups found to be superior to placebo were CBT and CBT+placebo, not the medication groups, whether combined with CBT or not.

In sum, results of the Barlow et al.[10] study suggested that results of the combined treatment were not fully maintained during follow-up. These findings have led Otto et al. to suggest that the combined treatment may "sap some of the stronger effects of CBT over time" [11, page 78]. Such a falling-off in gains of the combined treatment is explained by Otto et al.[11] and others from the following theoretical viewpoint. According to the cognitive behavioral model, patients receiving CBT have tested and disconfirmed their feared catastrophes regarding feared bodily sensations (interoceptive exposure) and feared situations (exposure in vivo). In this way, a sense of safety is relearned.[7] However, animal[12] and human studies[13] suggest that this relearning of safety is context dependent. [14;15] Context refers to aspects of the external world, but also to an internal state. This means that when safety is learned within a medicated state, as in a combined CBT and antidepressant treatment, safety might be abated once the medication is withdrawn. A combined treatment may thus result in relapse after discontinuation of the medication due to a shift in context. [11;16] We will refer to this as the 'context-safety hypothesis'.

In the present study, we compared the differential long-term effectiveness of CBT, SSRI, and the combination of both (CBT+SSRI). Several clinical trials have shown each of these treatment modalities to be superior to placebo. Our goal was to compare the differential effectiveness of these treatment modalities in a more naturalistic setting. Patients with panic disorder with or without agoraphobia (AG) were treated at both academic and non-academic clinical sites in the Netherlands. Follow-up assessments were scheduled at six and twelve months after treatment discontinuation. Results after nine months of treatment were previously reported[17]. Primary objective of the present study was to examine the differential long-term effectiveness of the three treatment modalities with the ultimate goal of

determining the most effective treatment for PD with or without AG. In light of the context-safety hypothesis, a fall-off in gains of the combined treatment after medication taper was expected and subsequently CBT was expected to have more durability during follow-up than either SSRI or CBT+SSRI. As a secondary objective, the relationship between treatment outcome and seven predictor variables was investigated. These variables were chosen based on previous studies (for a review see [18;19]) and include treatment site, baseline agoraphobia, duration of illness, Axis I en Axis II comorbidity, additional benzodiazepine use, and additional treatment during follow-up.

METHOD

Participating patients in each treatment modality received one year of treatment, including three months of tapering in case of SSRI use. They were seen twice during the subsequent follow-up year. Patients received either CBT, SSRI, or CBT+SSRI and were assessed before starting treatment (pretest), after nine months of treatment (posttest 1), immediately after discontinuation of treatment (posttest 2), and six and twelve months after treatment discontinuation (follow-up 1 and follow-up 2). In between pretest and posttest 1, patients received 18 CBT and/or 9 SSRI sessions. In between posttest 1 and posttest 2, CBT patients received additional booster sessions resulting in up to 21 CBT sessions from pretest to posttest 2. SSRI patients tapered their medication during this period in which three additional sessions were scheduled resulting in up to 12 SSRI sessions from pretest to posttest 2.
The CBT protocol is based on the work of Clark, Craske, and Barlow. [20;21] Patients in the CBT group received up to 21 CBT sessions each lasting approximately 50 minutes. The SSRI treatment was described in a treatment manual and was based on the guidelines as formulated by the Dutch Psychiatry Association regarding pharmacotherapy for anxiety disorders. [22] Pharmacotherapists were instructed to withhold from therapeutical interventions to avoid hidden exposure.

Assessment

Primary outcome measures

The Hamilton Anxiety Rating Scale (HAM-A) [23] assesses general aspects of anxiety and was administered by trained research assistants. A higher score represents a higher degree of anxiety (range 0-56).

The coping scale of the Panic Appraisal Inventory (PAI) [24] assesses the degree of confidence in coping with future panic attacks. Reliability and validity of the PAI were established and especially the coping scale proved sensitive to treatment effects. [25;26] PAI Coping scores range from 0 to 100; a higher score representing better coping.

Patients were defined remitters according to the definition of high end-state functioning previously used by Roy-Byrne et al. [27] Patients had to meet all three of the following criteria: free of panic attacks, minimal anticipatory anxiety, and minimal agoraphobia. In the present study, these criteria had to be met in the following way: To meet the first criterion, patients had to report no panic attacks in a panic-log during the two-week posttest 2 assessment. Anticipatory anxiety was measured by the PAI anticipated panic scale.[24] In order to meet the second criterion, there had to be a clinically significant change on the PAI anticipated panic scale according to guidelines as set forth by Jacobsen and Truax.[28] Finally, an agoraphobia subscale score of 10 or less on the Fear Questionnaire[29] was needed to meet the third criterion. The resulting primary outcome measure remitter status was dichotomous: remitter or no remitter.

Secondary outcome measures

Health related quality of life was measured by the RAND-36,[30] a commonly used multidimensional self-report questionnaire assessing eight domains of health-related

quality of life which yields two summary scales: physical health and mental health. Each summary scale (RAND–P (Physical) and RAND–M (Mental)) generates a (transformed) score ranging from 0 to 100 with a higher score representing better health. The RAND-36 was completed at pretest, at posttest 2, and at follow-up 2.

To control for comorbid depression, the Hamilton Depression Rating Scale (HAM-D: range 0-52) [31] was administered together with the HAM-A.

The extent to which patients were satisfied with the received treatment was assessed (at posttest 2) with the Client Satisfaction Questionnaire (CSQ).[32] The mean CSQ score ranges from 1 to 4 with a higher score representing a higher degree of satisfaction.

Predictor variables

Screening of participating patients consisted of a structured interview, the M.I.N.I., [33] checking DSM-IV criteria for Axis I disorders. Axis I comorbidity was thus established based on this interview. Axis II comorbidity was assessed by means of a self-report questionnaire which patients completed at pretest. This ADP-IV[34] (*A*ssessment of *D*SM-IV *P*ersonality disorders) was designed to prevent overdiagnosis by additionally assessing distress/impairment characteristics of each DSM-IV criterion. AG level was assessed, after inclusion, by the first author based on chart review and the structured interview. Patients were classified as not suffering from AG, or suffering from mild, moderate or severe AG following guidelines set forth by the DSM-III-R.

Statistical Analyses

In order to obtain a proper comparison between treatments, we distinguish three types of patients: completers, dropouts, and no-tapers. Patients were defined completers when treatment had ended with therapist consent. Also, completer patients received a minimum of 15 out of 21 CBT sessions and/or 8 out of 12 SSRI

sessions. Dropouts were lost during the first treatment year because of various reasons (see section 'attrition'). No-tapers failed to taper medication and used an SSRI throughout the entire study period.

To investigate and compare the effects of the three treatments over time, multilevel modeling was used.[35;36] Three models were build for respectively the PAI Coping scale, the HAM measures (A and D), and the RAND measures (P and M). The latter two models involve a joint modeling of two outcome measures in a three-level model, to account for dependencies between those measures. In the multilevel models, the statistical significance of the fixed regression effects is tested using the approximate t-test, and of the random effects using the deviance test. For each of the three models, the modeling strategy was as follows: Firstly, an adequate representation of the variance structure of the repeated assessments was found using dummy variables for posttest 1, posttest 2, follow-up 1 and follow-up 2. The dummy variables were coded such that each parameter expresses the change between the measurement concerned, and its predecessor. Because it was expected that no important changes in scores would occur between posttest 2 and follow-up 1, the differential effect follow-up 1 was retained only when significant. Secondly, initial and differential effects of treatment across time were examined using two dummy variables for treatment, and in interaction with the four assessment dummies. Because of the randomization, no differences across treatments are expected at pretest, and the effect of pretest was only preserved when significant. To show possible differential effects across time, interactions between treatment and posttest 1 were always included in the model; the remaining interaction effects were preserved only when significant. Thirdly, it was assessed whether those who completed the study differed from those who dropped out or those who failed to taper medication, using dummy variables. Possible differential effects across time and treatment were examined, but those effects were preserved only when significant. Fourthly, possible effects of treatment site, baseline agoraphobia, duration of illness, Axis I en Axis II comorbidity, additional benzodiazepine use, and

additional treatment during follow-up were examined, both as main effect and as interaction with received treatment. As random effects, the between-individual and within-individual variance were estimated. Random effects for the difference between pretest and posttest 1 were examined, and preserved when significant. All models were build using the program MlwinN. [37]

Univariate analyses of variance (ANOVAs) and posthoc bonferroni pair wise comparisons were used to evaluate pretest differences between patient groups, posttest 2 differences between satisfaction scores, and differences regarding duration of received treatment. Chi-square analyses were used to investigate overall differences in dropout-rate and remitter proportions. The differences between proportions were further evaluated by the Wilson 95% confidence interval (CI) around this difference. [38;39] Tests were two-tailed and alpha was set at .05.

RESULTS

Patient flow

After randomization, 150 out of 178 patients who were seen for screening (see flowchart Figure 4.1) received a pretest and started treatment. Several pretest characteristics of the present sample are presented in Table 4.1.

According to our definition of patient types, 83 out of 150 patients are defined completers. Further, 14 out of 150 patients are defined no-tapers. These patients started with an SSRI treatment (either randomized to SSRI or to CBT+SSRI) but never tapered their medication during the course of the trial. Three of these made an attempt to taper their medication but failed, the other 11 never tried (refused) to taper their medication. Finally, 53 patients out of 150 did not complete treatment and dropped out during the first study year.

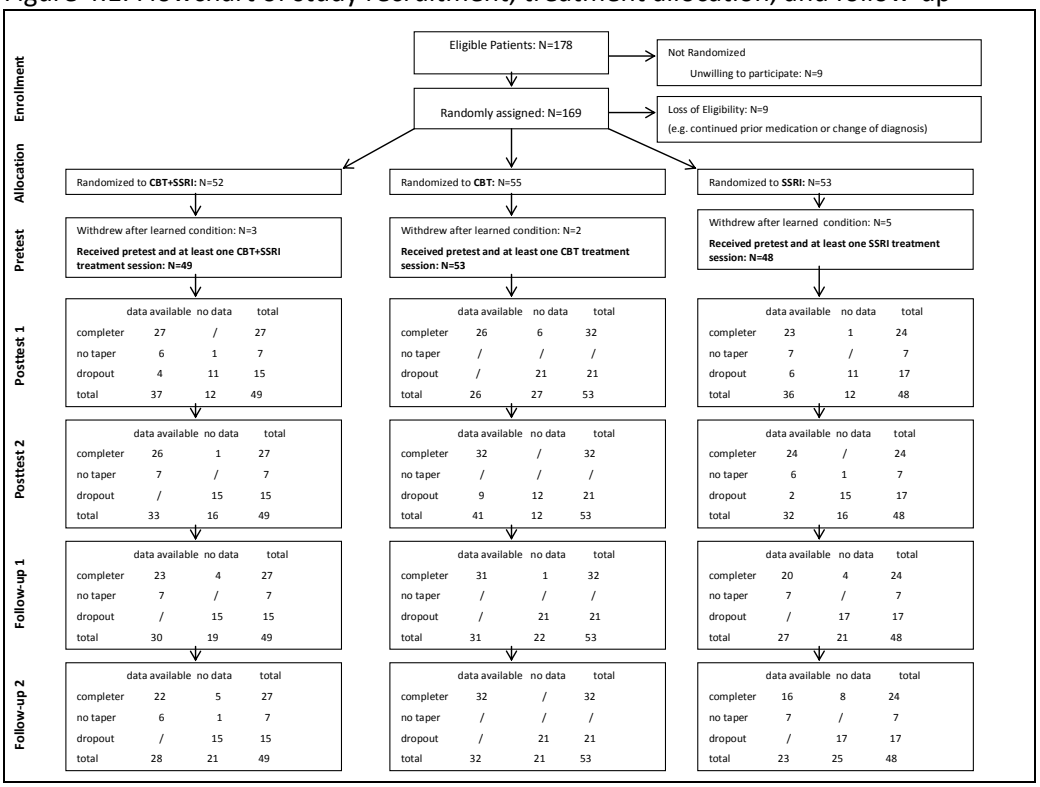
Table 4.1. Pretest characteristics for three groups

Pretest characteristic	CBT (n=53)		SSRI (n=48)		CBT+SSRI (n=49)		All Patients (n=150)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Duration of illness in years	8.1	8.4	10.2	10.4	7.2	7.6	8.5	8.9
Age	39.4	10.2	38.5	10.5	34.4	10.6	37.5	10.6
Number of panic attacks*	5.44	9.57	3.62	4.50	5.08	5.75	4.74	6.99
	n	%	*n*	%	*n*	%	*n*	%
Female sex	33	62.3	26	54.2	23	46.9	82	54.7
Currently married**	29	54.7	33	68.8	25	51.0	87	58.0
Currently employed	30	56.6	31	64.6	31	63.3	92	61.3
Level of completed education :								
low	10	18.9	11	24.4	11	22.4	32	21.8
moderate	28	52.8	16	35.6	14	28.6	58	39.5
above moderate	6	11.3	9	20.0	9	18.4	24	16.3
high	9	17.0	9	20.0	15	30.6	33	22.4
Level of agoraphobia (AG):								
no or mild AG	26	49.1	23	47.9	23	46.9	72	48
moderate or severe AG	27	50.9	25	52.1	26	53.1	78	52
Having received previous CBT treatment	2	3.8	3	6.4	7	14.3	12	8.1
Having received previous SSRI treatment	17	32.1	12	25.0	14	28.6	43	28.7
Comorbid Axis I disorder present	28	52.8	20	41.7	20	55.1	75	50.0

Notes: * mean number of panic attacks during two-week pretest period. ** or cohabiting with steady partner.

At follow-up 2, 12 months after treatment discontinuation, data was available for 83 patients of which 28 received CBT+SSRI, 32 received CBT, and 23 received SSRI (see Flowchart Figure 4.1). Patients not only dropped out during treatment (see "Attrition") but also during the second follow-up year: these patients did not attend follow-up(s) despite efforts from the research team to contact them. In the SSRI group, eight patients were lost during the follow-up year, and in the CBT+SSRI group six patients. All completer patients in the CBT group stayed in the study during the follow-up year.

Figure 4.1. Flowchart of study recruitment, treatment allocation, and follow-up



Attrition

Fifty-three patients were lost during the first treatment year resulting in an observed total dropout rate of 35%. Reasons for dropout, and the rates per treatment are listed in Table 4.2. No pretest differences regarding patient characteristics and pretest scores on all outcome measures were found between patients who subsequently dropped out and patients who subsequently completed treatment (all $p \geq .27$).

Both the overall and pair wise differences between the three treatment groups regarding dropout rates proved non-significant (overall: $\chi^2 = .91$, df = 2, $p = .64$).

Table 4.2. Reasons for dropping out of study by treatment group (n=53 for total dropouts)

	CBT+SSRI	CBT	SSRI
Side effects of medication	4	/	7
Life event not related to treatment	/	3	1
Non-compliance	5	5	2
Other treatment needed	3	2	1
Loosing motivation because of good results	/	1	/
Dissatisfaction with obtained results	1	4	2
Using medication outside protocol	/	3	/
Unspecified reasons (unknown)	2	3	4
Total	n=15 (31% of CBT+SSRI group)	n=21 (40% of CBT group)	n=17 (35% of SSRI group)

Timing of treatment discontinuation

Posttest 2 (to be administered after 52 weeks) was rescheduled when treatment termination was delayed or advanced. The CBT completers (n=32) showed a mean number of 50.4 weeks (SD 10.8, range 28.1-82.6) between pretest and posttest-II. The SSRI completers (n=24) a mean of 61.4 weeks (SD 14.5, range 49.0-110.1), and the CBT+SSRI completers (n=27) 60.0 weeks (SD 9.8, range 49.3-88.6). The overall difference between groups regarding number of weeks proved significant (F=7.68, df=2, p=.001). Pair wise comparisons revealed that CBT lasted significantly shorter than both the SSRI and CBT+SSRI treatments (95% CIs of difference in mean: 2.1 to 17.3, and 3.3 to 18.8 weeks, respectively). Patients receiving an SSRI (either with or without CBT) thus needed more time to discontinue treatment as compared to patients receiving CBT-only.

Number of received sessions

CBT completers received a mean of 19.0 (SD 4.0, range 7-25)[3] sessions. SSRI completers received a mean of 11.6 (SD 1.3, range 9-15) sessions. CBT+SSRI completers received a mean of 18.6 (SD 3.01, range 11-22) CBT sessions and a mean of 11.8 (SD 1.3, range 9-14) SSRI sessions.

SSRI treatment and adverse effects

The five SSRIs in order of times prescribed are: paroxetine (prescribed to 31 patients), sertraline (23), fluvoxamine (22), citalopram (22), and fluoxetine (4)[4]. For paroxetine, the mean highest daily dosage throughout the treatment period was 30.0 mg daily (SD 11.4 range 10-50 mg). For sertraline this was 85.9 mg daily (SD 37.6, range 25-150 mg), for fluvoxamine 144.3 mg daily (SD 48.8, range 50-200 mg), for citalopram 29.0 mg daily (SD 13.0, range 10-60 mg), and for fluoxetine 32.5 mg daily (SD 18.9, range 20-60 mg). Adverse effects related to medication were recorded on a symptom-and-side effects checklist by the pharmacotherapist at each visit. Taking the five SSRIs together, the most frequent reported adverse effects include nervousness (reported by 72 patients, 79%), weakness/fatigue (reported by 71 patients, 78%), headache (reported by 62 patients, 68%), sweating (reported by 57 patients, 63%), and insomnia (reported by 55 patients, 60%). There were some differences in adverse effects between the different SSRIs, based on the top three most reported side effects for each SSRI. Anxiety and weakness/fatigue were frequently reported for all five SSRIs. Headache was frequently reported as well but with the exception of citalopram. Drowsiness was only reported for fluoxetine, memory problems only for paroxetine and nausea only for citalopram.

[3] In four CBT-only cases, therapist and patient both agreed that more treatment sessions were not applicable because of early treatment success. These CBT completer patients received less than 15 CBT sessions (7, 11, 12 and 14 CBT sessions respectively).

[4] Numbers based on prescription data differ from number of SSRI users as can be obtained from the flowchart. This is explained by both missing data and by the fact that some patients have switched from one SSRI to another and thus more than one SSRI was prescribed to those patients.

Outcome measures

Estimated coefficients and standard errors of the multilevel models that were build for the measures HAM-A, PAI Coping, RAND-M/P, and HAM-D, are depicted in Table 4.3. Figures 4.2, 4.3, 4.4, and 4.5 plot the model based estimated scores for HAM-A, PAI Coping, RAND-M/P, and HAM-D respectively, for a completer patient without or with only mild AG, without comorbid Axis I disorders, who does not or only occasionally uses benzodiazepines and who suffers from panic complaints for 8.22 years (which is the mean duration of complaints as observed in the sample). Observed proportion remitters are depicted in Table 4.4. Possible differences between patient groups will be discussed in the 'Dropouts and no-tapers compared to completers'-section.

Table 4.3. Estimated coefficients and standard errors of the hierarchical models for the measures HAM-A, PAI Coping, RAND-P, RAND-M, and HAM-D

	HAM-A		PAI Coping		RAND-P		RAND-M		HAM-D	
Fixed effects:	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Intercept (mean score at pretest, CBT)	19.7	1.2	44.0	2.4	70.1	2.1	53.5	2.1	11.8	0.9
Contrast posttest 1	-6.6	1.4	32.2	3.5	NA	NA	NA	NA	-3.5	1.0
Contrast posttest 2	-2.5	1.2	2.3	1.5	3.5	2.6	10.9	2.7	-2.0	0.9
Contrast follow-up 2	-2.4	0.9	0.4	1.6	4.4	2.1	7.6	2.3	-1.7	0.7
SSRI at pretest	….	…	…	…	…	…	…	…	…	…
CBT+SSRI at pretest	….	…	…	…	…	…	…	…	…	…
Contrast posttest 1 x SSRI	-3.9	1.5	-1.9	3.8	NA	NA	NA	NA	-2.0	1.0
Contrast posttest 1 x CBT+SSRI	-5.8	1.5	4.4	3.8	NA	NA	NA	NA	-3.8	1.0
Contrast posttest 2 x SSRI	3.5	1.6	…	..	7.4	3.5	7.1	3.6	2.0	1.2
Contrast posttest 2 x CBT+SSRI	3.7	1.6	…	…	7.8	3.4	5.6	3.5	2.6	1.1
Contrast follow-up 2 x SSRI	…	…	…	…	…	…	…	…	…	…
Contrast follow-up 2 x CBT+SSRI	…	…	…	…	…	…	…	…	…	…
Dropout	-1.9	1.8	2.2	2.9	-4.9	3.2	-6.4	3.2	1.3	1.1
No-taper	4.2	2.1	-6.0	4.7	-7.7	4.5	-7.6	4.4	3.6	1.5
Contrast posttest 1 X dropout	5.5	2.0	-16.3	5.0	…	…	…	…	3.0	1.4
Contrast posttest 1 x no-taper	…	…	-10.0	5.4	…	…	…	…	…	…
Duration of complaints	…	…	0.2	0.2	…	…	…	…	…	…
Contrast posttest 1 x duration of complaints	…	…	-0.5	0.2	…	…	…	…	…	…

Table 4.3. continued. Estimated coefficients and standard errors of the hierarchical models for the measures HAM-A, PAI Coping, RAND-P, RAND-M, and HAM-D

	HAM-A		PAI Coping		RAND-P		RAND-M		HAM-D	
Fixed effects:	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Level of Agoraphobia	…	…	-9.6	2.4	…	…	…	…	…	…
Comorbid Axis-I disorder	5.7	1.5	…	…	…	…	…	…	4.0	1.0
Contrast posttest 1 x Comorbid Axis-I disorder	-3.7	1.3	…	…	…	…	…	…	-2.9	0.9
Comorbid Axis-II disorder	…	…	…	…	…	…	…	…	…	…
Benzodiazepine use	…	…	-9.6	3.3	-16.4	4.0	-15.5	4.1	…	…
Random effects:										
Between individual variance	43.1	6.6	117.4	24.8	168.7	32.0	146.9	31.2	20.9	3.2
Covariance between dependent variables	28.1	4.4	…	…	…	…	121.9	26.9	…	…
Additional variance of contrast posttest 1	…	…	141.7	34.6	…	…	…	…	…	…
Residual variance at measurement occasions	38.2	2.8	125.8	10.6	192.2	20.1	220.3	22.9	18.7	1.4
Covariance between dependent variables at measurement occasions	20.6	1.7	…	…	…	…	106.9	17.1	…	…

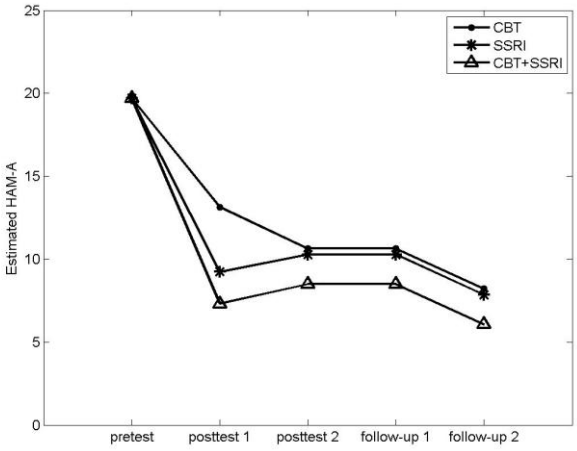
Note: NA = Not Applicable, S.E.= Standard Error, HAM-A = Hamilton Anxiety Rating Scale, PAI = Panic Appraisal Inventory, RAND-P= summary scale physical health-related quality of life, RAND-M= summary scale mental health-related quality of life. HAM-D= Hamilton Depression Rating Scale; contrast at a measurement occasion is the contrast between the measurement occasion and previous test occasion(s)

Primary outcome measures

HAM-A

As can be derived from Table 4.3 and as depicted in Figure 4.2, on the HAM-A, CBT+SSRI outperforms CBT (and to a lesser extent SSRI) up to posttest 1, hence while treatment is continued. After treatment discontinuation however, CBT catches up and the monotherapies run on parallel tracks from posttest 2 up to follow-up 2. All treatment groups improved significantly from pre- to posttest 1. The improvement for the CBT group from posttest 1 to posttest 2 was significant as well. The slight increase observed from posttest 1 to posttest 2 for the CBT+SSRI and SSRI groups, proved non-significant. All treatment groups improved significantly from posttest 2 to follow-up 2. At posttest 1, pair wise comparisons revealed that both CBT+SSRI and SSRI were superior to CBT. This superiority was no longer observed at subsequent assessments when all pair wise differences between treatment modalities proved non-significant.

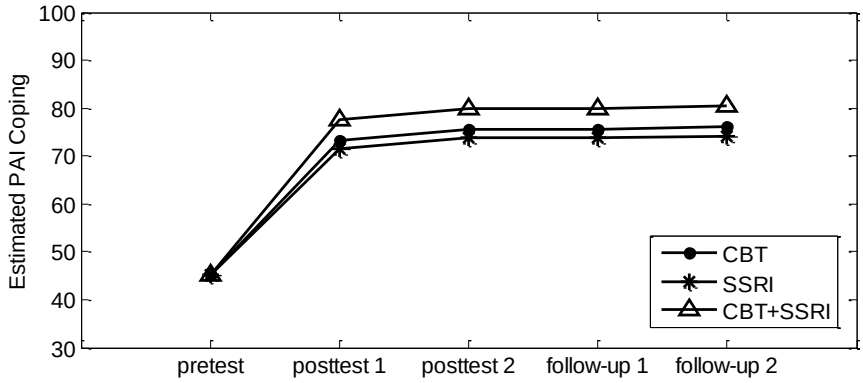
Figure 4.2. Model-based estimated scores for the HAM-A by treatment group



PAI Coping

Regarding PAI Coping (see Figure 4.3), all treatment groups improved significantly from pre- to posttest 1 and no significant changes were observed after posttest 1 up to follow-up 2. This means that all treatment modalities were associated with an increased confidence in coping with future panic attacks and this effect was maintained throughout treatment and follow-up. Although visual inspection of the plot in Figure 4.3 reveals higher coping scores for CBT+SSRI as compared to the monotreatments, no significant differences between treatment modalities were observed for PAI Coping at any assessment.

Figure 4.3. Model-based estimated scores for PAI Coping by treatment group



Remitter status

Table 4.4 shows the number of observed remitters in the completer group at four assessments. To assess possible differences between treatment modalities regarding remitter proportions, four Chi-square analyses (one for each assessment) were performed. These analyses revealed no significant differences at any assessment (all $p \geq .07$).

Table 4.4. Remitter status for completer patients at four assessments

	Meeting Remitter criteria (Yes or No)					
	CBT+SSRI		CBT		SSRI	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Posttest 1	14 (52)	13 (48)	6 (19)	20 (63)	11 (46)	12 (50)
Posttest 2	14 (52)	11 (41)	14 (44)	18 (56)	8 (33)	15 (63)
Follow-up 1	10 (37)	12 (44)	14 (44)	16 (50)	6 (25)	14 (58)
Follow-up 2	13 (48)	9 (33)	10 (31)	20 (63)	6 (25)	10 (42)

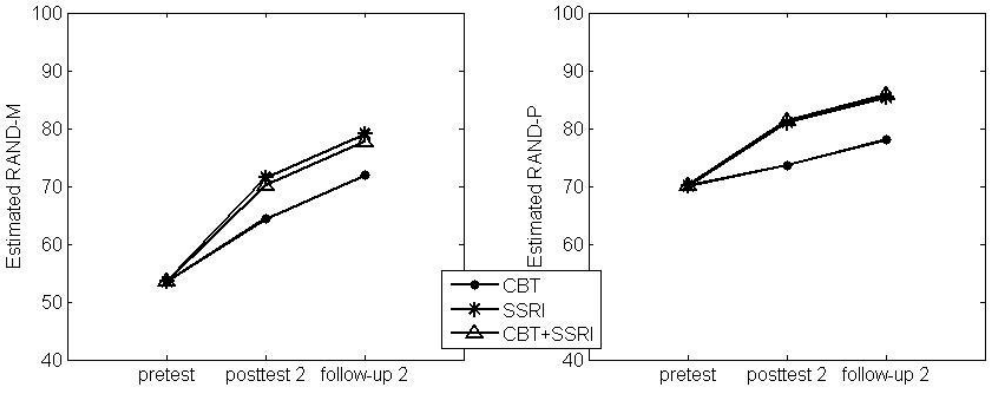
Note: CBT+SSRI: n=27, CBT: n=32, and SSRI: n=24. Completer patients for who remitter status could not be established due to incomplete data were excluded from this Table.

Secondary outcome measures

Health related quality of life

As can be seen from Figure 4.4, at pretest physical health scores were higher as compared to mental health scores. This suggests that our sample of patients experienced problems regarding their mental health but not as much regarding their physical health. Estimated health scores were consistently lower for CBT patients as compared to SSRI and CBT+SSRI patients both regarding physical and mental health. For RAND-P, the improvement from pretest to posttest 2 was significant for the SSRI and CBT+SSRI groups but not for the CBT group. All treatment groups improved significantly from posttest 2 to follow-up 2. Pair wise comparisons revealed that both CBT+SSRI and SSRI were superior to CBT at posttest 2 and follow-up 2. For RAND-M, all treatment groups improved significantly from pretest to posttest 2 and from posttest 2 to follow-up 2. Pair wise comparisons revealed that SSRI (but not CBT+SSRI) was superior to CBT at posttest 2 and follow-up 2.

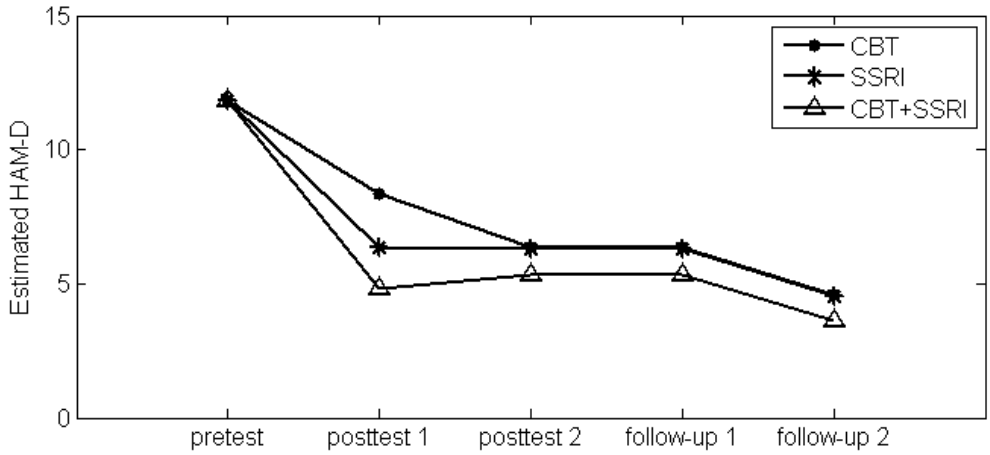
Figure 4.4. Model-based estimated scores for the RAND-M (left) and RAND-P (right) by treatment group



Hamilton Depression

As can be seen in Figure 4.5, the pattern of results for the HAM-D generally matches the results as described for the HAM-A however, HAM-D scores were lower to begin with in our sample of patients. Also, differences between treatment modalities were even smaller as indicated by almost perfect parallel tracks. All treatment groups improved significantly on the HAM-D from pretest to posttest 1. Subsequently, CBT improved significantly from posttest 1 to posttest 2 while posttest 1 – posttest 2 differences proved non-significant for the CBT+SSRI and SSRI groups. All treatment groups improved significantly from posttest 2 to follow-up 2. Pair wise comparisons revealed that at posttest 1, CBT+SSRI was superior to CBT. This superiority could not be confirmed at subsequent assessments when pair wise differences between treatment modalities proved non-significant.

Figure 4.5. Model-based estimated scores for the HAM-D by treatment group



Client Satisfaction

At treatment endpoint, patients completed the CSQ and the following means were established for the completer group: for CBT+SSRI: 3.62 (SD .39), for CBT: 3.29 (SD .48), and for SSRI 3.40 (SD .55). Given that the mean CSQ score ranges from 1 to 4, our sample of patients can be considered highly satisfied with the received treatment.[32;40] Overall differences proved significant between treatment groups ($F=4.45$, $df=2,106$, $p=.014$). Subsequently, posthoc analyses revealed significant differences between CBT+SSRI and CBT (95% CI of difference: 0.06 to 0.60) implying that patients having received CBT+SSRI appear slightly more satisfied with treatment as compared to patients having received CBT-only. Finally, patients obtained equivalent high mean CSQ scores regardless of type of site in which they were treated, and regardless of whether they were treated by student-therapists or qualified therapists (all $p \geq .74$).

Dropouts and no-tapers compared to completers

The variable 'type of patient' categorized patients into completers, dropouts, and no-tapers. A main effect of dropout was found for the measure RAND-M which implies that dropout patients reported overall lower mental health scores as compared to completer patients. A main effect of no-taper was found for the measures HAM-A and HAM-D which implies that patients who failed to taper medication were associated with overall higher anxiety and depression levels as compared to completer patients. On no measure, an interaction effect between type of treatment and type of patient was observed which means that the effect of type of patient could not be shown to differ between treatments. At posttest 1, the difference between completers and dropouts was significant for PAI Coping, HAM-A, and HAM-D suggesting that from pretest to posttest 1, dropout patients had experienced a smaller decrease in anxiety and depressive complaints, and a smaller increase in coping, as compared to completer patients. Regarding treatment satisfaction, mean CSQ scores were compared. The mean for the completer group was 3.54 (SD .41), for dropouts 2.94 (SD .59), and for no-tapers 3.29 (SD .54). Overall differences proved significant between patient groups ($F=10.37$, $df=2$, $p < .001$). Subsequently, posthoc analyses revealed significant differences between the completers and the dropouts (95% CI of difference: 0.27 to 0.93) implying that patients who had completed treatment were more satisfied with treatment as compared to patients who had dropped-out of treatment.

Predictor variables

Site effects

Sixty-three patients were treated at the two university training and research centers, 42 at the two university research clinics, and 45 patients at the seven regular mental health clinics. Previous analyses[17] revealed no differences between the three kinds of participating sites regarding pretest scores, dropout-rate, and treatment effect at posttest 1. In the present analyses, again no effect of site was found for any of the outcome measures at any assessment.

No/mild versus moderate/severe AG

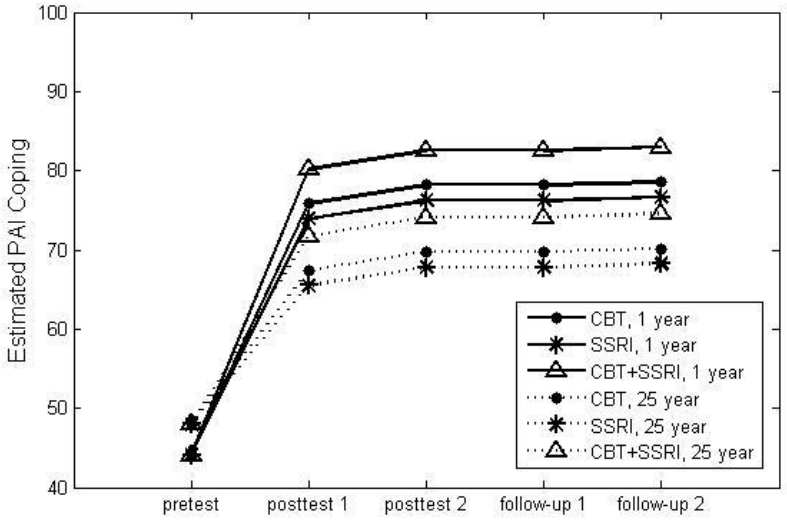
About half of the patients in the present sample did not suffer from AG or suffered from only mild AG (48%) while the other half suffered from moderate or severe AG (52%). Only for the primary outcome measure PAI Coping, a significant main effect of AG status (no/mild vs. moderate/severe) was found indicating that patients with moderate/severe AG reported less confidence in their ability to cope with future panic attacks as compared to patients without or with only mild AG.

Duration of illness

At pretest, the number of years that patients suffered from their complaints ranged from six months to 43 years (mean: 8.23, SD: 8.53). For PAI Coping, a significant relationship was found between duration of illness, treatment effect over time and the level of confidence in the ability to cope with future panic attacks. At pretest, patients who had suffered from their PD complaints longer reported on average more confidence in their coping abilities as compared to patients who had suffered from their PD complaints for a shorter period of time. However, the increase in

confidence reported from pretest to posttest 1 appeared significantly lower for the longer suffering patients resulting in higher coping scores at subsequent assessments for the patients who suffered from their PD complaints for a shorter period of time. To illustrate this phenomenon, Figure 4.6 shows the model based estimated PAI Coping scores for the three treatment modalities when panic complaints were present for one year at the time of the intake and for twenty-five years.

Figure 4.6. Model-based estimated PAI Coping scores for 3 treatment modalities for panic disorder duration of 1 year and 25 years



Axis I Comorbidity

Presence of comorbid Axis I disorders was checked for at intake. At that time, 50% (n=75) suffered from at least one additional Axis I disorder according to the standardized interview.

On both Hamilton scales, patients with (at least one) comorbid Axis I disorder

reported significantly more anxious and depressive complaints at pretest as compared to patients with no comorbid Axis I disorder. At posttest 1, the difference between patients with and without comorbid Axis I disorders had become smaller but was still significant. The difference was maintained at subsequent assessments.

Axis II Comorbidity

Axis II disorders were not formally diagnosed but a screening self-report questionnaire[34] was completed at pretest. At that time, 20% of the patients met the criteria of at least one Axis II disorder. There were no differences between treatment groups (χ^2 = .03, df=2, p =.99). No main effect (or interaction effect with time of assessment) of Axis II comorbidity was found on any outcome measure.

Additional benzodiazepine use

According to protocol, patients were not allowed to use psychotropic drugs except small doses of benzodiazepines (maximum the equivalent of 20 mg oxazepam per day). Benzodiazepine use was scored on a 4 point scale, with 1 being 'none', 2 'only infrequently', 3 'regularly, but not daily', and 4 'daily'. The multilevel models for all measures revealed that patients scoring 1, 2, or 3 showed similar patterns of response and therefore these were pooled in the so called 'no or occasional benzo' group. This group of patients was compared to the patients that used benzodiazepines on a daily basis; the 'daily benzo' group. The multilevel models revealed that using benzodiazepines on a daily basis proved to be a factor of importance as reflected on the measures PAI Coping and RAND-M/P. On these measures, a significant main effect of additional benzodiazepine use was observed indicating that overall (in the same degree at each assessment) patients in the 'daily benzo' group reported lower health scores and less confidence in their ability to

cope with future panic attacks as compared to patients in the 'no or occasional benzo' group.

To gain insight in the frequency of benzodiazepine use across treatment modalities and assessments, benzodiazepine use is summarized in Table 4.5. It seems that, once treatment has started, a little more CBT-only patients use additional benzodiazepines as compared to patients using an SSRI, either combined with CBT or not. The majority of patients however (63% of completer sample), does not use any additional benzodiazepines, at any assessment.

Table 4.5. Number of benzodiazepine users among completer patients by treatment group

	CBT+SSRI n (%)	CBT n (%)	SSRI n (%)	Total n (%)
No benzodiazepine use at any assessment	18 (67)	20 (63)	14 (58)	52 (63)
Benzodiazepine use at pretest and at least at one subsequent assessment no benzodiazepine use	8 (30)	4 (13)	9 (38)	21 (6)
No benzodiazepine use at pretest and benzodiazepine use at least at one subsequent assessment	1 (3)	3 (10)	1 (4)	5 (6)
Benzodiazepine use at each assessment	/	5 (16)	/	5 (25)
Total	27	32	24	83

Note: Only completer patients are included. Benzodiazepine use could vary between very infrequent use to daily use.

Additional treatment during follow-up

For the patients who completed treatment and were assigned to follow-up, it was recorded whether additional treatment was received during follow-up. Of the completer sample, 64% (n=53) received no additional treatment during follow-up, 23% (n=19) did receive additional treatment during follow-up, and information regarding additional treatment during follow-up was missing for 13% (n=11). With respect to the different treatment modalities, nine CBT+SSRI patients (33%) received additional treatment, five patients in the CBT (16%), and five patients (21%) in the SSRI group. The nine CBT+SSRI patients with additional treatment received CBT (n=2), an SSRI (n=5), a combined CBT+SSRI treatment (n=1), or a psychological treatment other than CBT (n=1). The five CBT patients with additional treatment received an SSRI (n=3) or a combined CBT+SSRI treatment (n=2). The five SSRI patients with additional treatment received CBT (n=2), SSRI (n=2), or both CBT and SSRI but not simultaneously (n=1). CBT+SSRI thus yielded the highest and CBT the smallest proportion of patients receiving additional treatment during follow-up. The overall difference proved non-significant ($\chi^2 = 4.3$, df=2, p =.12). Subsequent pair wise comparisons of proportions revealed an almost significant difference between CBT+SSRI and CBT (95% CI of difference in proportion from -.04 to 0.39) which might be indicative of a trend.

The variable 'additional treatment' was included in the multilevel models to investigate the possible influence of receiving additional treatment during follow-up on long-term treatment outcome. No main effect (or interaction effect with time of assessment) of additional treatment was found on any outcome measure.

DISCUSSION

Based on the context-safety hypothesis, we expected CBT to have more durability during follow-up than CBT+SSRI and SSRI. However, no significant loss of gains after treatment discontinuation was observed for either treatment modality. One-year follow-up results suggested that the three treatment modalities were generally equally effective. Major changes occurred during the first nine months of treatment during which all three treatment modalities were associated with statistically significant, and clinically relevant, improvement on all outcome measures. Subsequently, results were maintained during follow-up. On the measures HAM-A, HAM-D, and RAND-M/P, even further improvement during follow-up was observed.

When pair wise evaluating treatment modalities, most differential effects were observed during the first treatment year. Significant differences on the primary outcome measures were observed at posttest 1 when SSRI and CBT+SSRI proved superior to CBT on the HAM-A. Subsequently, significant differences between treatment modalities were no longer observed at follow-up 2, twelve months after treatment discontinuation.

Results thus suggest that gains produced by CBT were slower to emerge than those produced by the other treatment modalities. The CBT treatment in the present study lasted one year, which is longer than the CBT in several other trials. In the Barlow et al. study, CBT lasted nine months. In the present study, at nine months CBT was not quite up to the level of the other treatments. Based on the comparison of effect sizes however, the CBT in the present study seems as effective as the CBT delivered in other trials. Previously, we reported an effect size of 0.60 for the CBT in the present study while we established an effect size of 0.62[17] for the CBT in the Barlow et al. study.[10]

Consistent with previous reports, CBT was able to maintain its gains through-out follow-up. More surprisingly however, SSRI alone was also not associated with a fall-off in gains and this is countering general consensus. It should be noted however that the general consensus is in part based on studies using benzodiazepines or antidepressant medication other than SSRI (e.g. imipramine). Studies presenting relapse rates after SSRI discontinuation are scarce. There is clearly a need for studies like the present, investigating the long-term effects of SSRIs following cessation of pharmacotherapy.

Considering the present results, we must conclude that we have not succeeded in determining *the* most effective treatment for PD with or without AG since no evidence was found for clear superiority of one treatment modality over another. Studies like the present should eventually result in recommendations that can be passed on to practitioners. [41] At this point however, we are not able to predict under what conditions and for which patients a stronger effect can be expected from a particular treatment modality. This leaves the practitioner with the task of making a thoughtful treatment selection for each individual patient. In this process, any previous patient experience with either treatment modality or a possible preference of the patient for either treatment modality can be taken into account. Also, taking into consideration some general drawbacks and plus points of each treatment modality might be helpful in selecting a treatment. In the present study, the delayed treatment effects associated with CBT might be considered a drawback of CBT-only. Plus points of CBT-only include the fact that it was not associated with adverse or withdrawal effects, and that treatment ended sooner (as in duration of treatment in weeks) than both the SSRI and CBT+SSRI treatments which is interesting from a cost-effectiveness perspective. An advantage of the SSRIs is the observed more immediate effect as compared to CBT-only. Also, the SSRI treatment consisted of half

the number of treatment sessions of the CBT treatment while maintaining its gains equally through-out follow-up. On the other hand, SSRIs are associated with adverse events which can be considered a drawback of medication treatment. Almost 80% of the patients using an SSRI in the present sample reported at least one adverse effect.

When comparing CBT+SSRI to SSRI-only, it seems that CBT was a valuable and perhaps even indispensable addition to a pharmacotherapeutical treatment because CBT+SSRI was associated with lower HAM-A and HAM-D scores, higher PAI Coping scores and more patients achieving remitter status at each assessment as compared to SSRI-only. From a cost-effectiveness perspective however, CBT+SSRI might be less attractive as compared to a monotreatment.

Seven predictor variables for treatment effect were investigated in the present study and some interesting findings emerged. Patients who suffered from their complaints for a longer period of time reported considerably less improvement regarding confidence in their coping abilities. Considering some preliminary evidence for the relationship between the related concept of self-efficacy scores and relapse,[42] it seems worthwhile to promote early treatment interventions.

Benzodiazepines are associated with the issues of dependence and withdrawal difficulties.[6] Present data suggest that using benzodiazepines on a daily basis is associated with lower health scores and lower coping scores as compared to no or infrequently benzodiazepine use. In the present sample however, only a few patients used additional benzodiazepines on a daily basis. This might imply that when receiving adequate treatment, patients generally do not need additional benzodiazepines.

Twenty-three percent of the completer patients were in need of additional treatment during the one-year follow up period. Data on this subject from other studies is limited. About half of the patients received treatment during follow-up in

the study by Sharp et al.[43] who stated that patients receiving post-study treatment should be excluded from follow-up analysis. In the present study however, no relationship between receiving additional treatment and treatment outcome was found. According to the context-safety hypothesis, one would expect more CBT+SSRI than CBT-only patients to require additional treatment during follow-up. Although we found some indications for this in the present data, results were non-significant. At least as interesting is the finding that, just as in the CBT group, only five patients in the SSRI condition received additional treatment during follow-up. At the moment, we cannot explain the difference between SSRI and CBT+SSRI regarding additional treatment during follow-up. Patients in the SSRI group experienced a shift of context when discontinuing medication just as patients in the CBT+SSRI group but less patients apparently were subsequently in need of additional treatment. Because the small numbers involved and the non-significance of the findings, future studies should again take this matter under scrutiny.

Strengths of the present study include the naturalistic character of the study, the fact that clinical sites as well as research sites participated, and the resulting high generalizability of findings. Also, our follow-up period was twice as long as previously reported studies[10;43] thereby yielding more insight into the long-term effectiveness of treatments. Further, patients with moderate or severe AG were not excluded and results are thus generalizable to the whole AG continuum. Next, predictor variables were investigated in order to further clarify outcome. Finally, because we did not only look at differences between treatment modalities but also differentiated between different patients groups (completers, dropouts, and no-tapers), we were able to study specific treatment-patient interactions. Regarding this issue, please note the applied strict definitions of dropouts and completers. In the present study, a patient who received fourteen CBT sessions and subsequently terminated

treatment without therapist consent was considered a dropout while in some other studies[43] such a patient would be categorized as a completer. We choose for this definition in order to ensure a homogeneous completer group but recognize that this has increased our number of dropouts.

Several limitations deserve mention. First, a binary variable such as remitter status naturally suffers from a loss of power. Furthermore, because remitter status is a composite measure, information on the effectiveness in terms of its separate constituents (agoraphobic avoidance, anticipation anxiety, and panic attacks) is lost. Second, the research assistants who administered the HAM-A and the HAM-D were thought to be independent and not partial to either treatment modality. However, they were not blind regarding allocation status and this presents a possible source of bias. Third, treatment adherence was checked by evaluating detailed forms regarding session content as completed by all therapists following each treatment session. We refrained from more formal treatment integrity and fidelity checks because this was considered to be incompatible with our intention to simulate clinical practice. Although these evaluations revealed no deviations from the treatment manuals, we realize that checking treatment integrity in this way is not soundproof. Finally, the present sample size was limited as compared to e.g. the sample size in the study by Barlow et al.[10] This means that we must take into consideration the possibility that some effects were non-significant due to a lack of power.

The present findings could not confirm the context-safety hypothesis. Previous work suggests that context may refer to an internal state implying that when safety is learned within a medicated state, safety is abated once the medication is withdrawn. However, an internal state might be defined not simply by the presence or absence of medication but rather by how the use of medication is explained by

the individual patient. Context may thus refer to an internal state which in turn is defined by the individual attribution of improvement. If improvement is attributed solely to the medication then relapse following medication taper is to be expected. If, however, improvement is attributed to both CBT and SSRI, an internal state might not change so radically when tapering medication. This may explain observed differences between the combined treatment and the SSRI as a monotreatment. Some preliminary findings[44] to date warrant further work into this matter.

In conclusion, the present findings indicate that both CBT-only, SSRI-only, and CBT+SSRI are effective treatments for PD with or without AG. Future research should continue to strive for a better understanding of the role of predictor variables and specific working mechanisms associated with different treatment modalities in order to aid the practitioner in the process of treatment selection.

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CHAPTER 5

RATE OF IMPROVEMENT DURING AND ACROSS TREATMENTS

This chapter is a slightly altered version of a previous publication:
Rate of improvement during and across three treatments for panic disorder with or without agoraphobia: Cognitive behavioral therapy, selective serotonin reuptake inhibitor or both combined.
Franske J. van Apeldoorn, Wiljo J.P.J. van Hout, Marieke E. Timmerman, Peter Paul A. Mersch, Johan A. den Boer (2013).
Journal of Affective Disorders; 150(2): 313-319.

ABSTRACT

Existing literature on panic disorder yields no data regarding the differential rates of improvement during CBT, SSRI or both combined. The main objective of the present study was to examine the rate of improvement in panic attack frequency during treatment and the relationship between rate of improvement and baseline AG. Patients were randomized to receive CBT, SSRI or CBT+SSRI which each lasted one year including three months of medication taper. Participating patients kept record of the frequency of panic attacks throughout the full year of treatment. A significant decline in frequency of panic attacks was observed for each treatment modality. SSRI and CBT+SSRI were associated with a significant faster rate of improvement as compared to CBT. Gains were maintained after tapering medication. For patients with moderate or severe AG, CBT+SSRI was associated with a more rapid improvement on panic frequency as compared to patients receiving either monotreatment. In conclusion, patients with PD responded well to each treatment as indicated by a significant decline in panic attacks. CBT was associated with a slower rate of improvement as compared to SSRI and CBT+SSRI. Discontinuation of SSRI treatment did not result in a revival of frequency of panic attacks. Our data suggest that for patients without or with only mild AG, SSRI-only will suffice. For patients with moderate or severe AG, the combined CBT+SSRI treatment is recommended.

INTRODUCTION

CBT and SSRIs are now widely accepted as the gold standard for the treatment of panic disorder (PD).[1] In naturalistic settings, many patients receive a combination of these two treatment modalities. A handful of randomized trials have performed head-to-head comparisons between CBT and antidepressants for PD[2-9] but only three of these studies compared both monotreatments (CBT-only and antidepressants-only) with the combination of both within a single design allowing for an optimal comparison.[3,6,7]

We previously reported on the differential long-term effectiveness of CBT, SSRI, and the combination of both (CBT+SSRI) in the treatment of PD with or without AG.[5] Patients were treated at both academic and non-academic clinical sites in the Netherlands. Patients received one year of treatment, including medication taper in case of SSRI use. Results from pre-, and posttest outcome measures suggested that gains produced by CBT were slower to emerge than those produced by the other treatment modalities. Follow-up results revealed no fall-off in gains for either treatment modality after treatment discontinuation. However, to obtain a detailed insight into symptom changes in the course of therapy and relate those changes to treatment modalities, intensive measurement across time is needed. Surprisingly, the existing literature on PD yields no actual data regarding the differential rates of improvement during CBT-only, SSRI-only and the combination of both. There is some evidence from treatment outcome studies (e.g., Sharp et al., 1996) suggesting a more rapid improvement for a combined CBT and SSRI treatment but rate of improvement was not fully investigated in these studies. Rate of improvement is however considered to be a critical clinical variable as rapid improvement not only diminishes ongoing suffering, but may also prevent attrition.[10]

The primary goal of the present study is to gain insight into the rate of improvement both during and across the currently most effective treatments for panic disorder. As primary measure that reflects symptom change during treatment and that can be measured intensively, we choose frequency of panic attacks. The occurrence of panic attacks is a core symptom of PD and contributes greatly to the suffering of PD patients. PD patients are thought to reliably indicate the presence or absence of panic attacks.[11] Panic attack frequency was examined for the period of one year in which treatment was delivered including medication taper.

Research goals for the present study are: 1. To examine the rate of improvement in panic attack frequency during treatment. We expect patients to improve significantly as indicated by a decline in the number of panic attacks in all three treatment modalities. 2. To determine possible differential effects in rate of improvement across treatment modalities. Based on previous results regarding differential treatment effectiveness, analyzing pre- and post-outcome data,[5,6] we expect patients receiving an SSRI (either as monotreatment or in combination with CBT) to show a faster rate of improvement as compared to patients receiving CBT-only. 3. To examine the effect of tapering medication across treatment modalities. From week 40, patients receiving an SSRI, either as monotreatment or combined with CBT, tapered their medication. Several authors suggest that patients are more prone to relapse following medication discontinuation due to a shift in context.[12-14] We previously referred to this theoretical frame-work as the 'context-safety hypothesis'[5] but our previous findings could not confirm this hypothesis. In the present study, we further examine this issue. In accordance to former hypothesis, an increase in number of reported panic attacks following medication taper is expected for patients who received either CBT+SSRI or SSRI. 4. To examine the relationship between rate of improvement in panic frequency and baseline severity of

agoraphobia. In most clinical outcome studies, the proportion of PD patients with AG exceeds those of PD without AG,[15] whereas some clinical trials excluded patients with agoraphobia altogether.[3] PD patients with AG are associated with a greater disability as compared to PD patients without AG.[15] The question whether treatment for PD patients should differ depending on the presence or severity of AG has been subject of debate. Results from a recent meta-analysis support the contemporary view that there is no reason to offer PD patients with AG a different kind of treatment than patients without AG.[16]

METHOD

Randomized patients met DSM-IV criteria for PD with or without AG as primary diagnosis. Patients were not required a minimum number of panic attacks during baseline. Participating patients in each treatment condition received one year of treatment. Patients received CBT, SSRI, or CBT+SSRI. For patients randomized to CBT+SSRI, the two treatments started simultaneously and were delivered parallel. AG level was assessed, after inclusion, by the first author based on chart review and a structured interview.[17] Patients were classified as not suffering from AG, or suffering from mild, moderate or severe AG following DSM-III-R definitions. Presence of panic attacks was assessed prospectively (i.e., using event-contingent recording): participating patients were asked to color a box in a panic plot each time a panic attack occurred. From those panic plots, we derived the frequency of panic attacks. Patients kept this panic plot through-out treatment and brought it to each treatment session: it was then showed to the therapist who copied the information to the therapist version of the panic plot. For analyses, scores were added up into weekly frequency scores.

Statistical Analyses

To investigate and compare the rate of improvement in frequency of panic attacks over time, two multilevel poisson models were build.[18,19] We used poisson regression to adequately model the counts (i.e., the discrete non-negative responses (0,1,....)). The statistical significance of the regression effects was tested using the approximate t-test, and alpha was set at 0.05. The modeling strategy to examine the rate of improvement, the effect of tapering medication and possible differential effects across treatments (research goals 1 to 3), resulting in Model I, was as follows: Firstly, an adequate representation of the variance structure of the repeated assessments was found using the following predictors (and its meaning in brackets): Intercept (week 0), Week (long-term changes), Lnweek (logarithm of week; short-term changes), Dcondition (dummy; differential effect of conditions at week 0), interactions of week with Dcondition, and Lnweek with Dcondition (differential effects of conditions in long-term and short-term changes, respectively), Dweek40 (dummy, change in effect at week 40), interactions of Dweek40 with Dcondition (differential effects of conditions in effect at week 40), interactions of Dweek40 with Dcondition and lnweek (differential recovery effects of conditions of change at week 40). Secondly, we retained the following effects (and their justification for not expecting) only when significant: Dcondition (due to random assignment, no initial differences expected), interaction Lnweek with Dcondition (if any, differential effects of conditions in long-term changes expected to suffice), Dweek40 (due to dummy coding, effect refers to CBT group, for which no tapering takes place).

To examine the relationship between rate of improvement of panic frequency and baseline severity of agoraphobia, we first removed from Model I non-significant effects to avoid instabilities of model estimates. Subsequently, we included the

following effects: AG status (dummy; differential effect of AG status at week 0), interactions of AG status with Week (differential effect of AG status in long-term changes), and interactions of AG status with Week with Dcondition (differential change effects of conditions and AG status), resulting in Model II.

All models were built using the program MlwinN. [20] In order to obtain a proper comparison between treatments, we distinguished three types of patients: dropouts, no-tapers, and completers. Dropouts were lost during the first treatment year because of various reasons such as non-compliance or needing other treatment. No-tapers failed to taper medication and used an SSRI throughout the entire study period. Patients were defined completers when treatment had ended with therapist consent. Also, completer patients received a minimum of 15 out of 21 CBT sessions and/or 8 out of 12 SSRI sessions. For the present analysis, only completer patients were included because the other groups were too small (regarding both numbers of patients and of available time points) to obtain reliable results (total panic logs available: for dropouts: CBT n = 17, SSRI n = 9, CBT+SSRI n = 11; for no-tapers: SSRI n = 6, CBT+SSRI n = 5). Further, data from one (CBT completer) patient was excluded from analyses, because the extremely high reported panic attack frequency (i.e., about 20 attacks per week) casted doubt on the score reliability. The number of panic logs present for analyses varied somewhat from week to week. Table 5.1 summarizes the number of available panic logs, as the mean number per treatment group for three time periods. To further evaluate differences between treatment groups per week, we used univariate analyses of variance (ANOVAs) and post-hoc pair wise comparisons, with bonferroni correction. Tests were two-tailed and alpha was set at .05.

Table 5.1. Mean numbers of available panic logs per week (min-max) at weeks 1-17, 18-35, and 36-52. n indicates total number of patients in sample

	CBT (n=32)	SSRI (n=24)	CBT+SSRI (n=27)
weeks 1 – 17	26.94 (25-29)	20.88 (20-21)	22.94 (22-23)
weeks 18 - 35	23.50 (22-25)	19.55 (19-20)	20.66 (20-23)
weeks 36 - 52	15.18 (7-21)	18.10 (17-19)	15.88 (8-20)

RESULTS

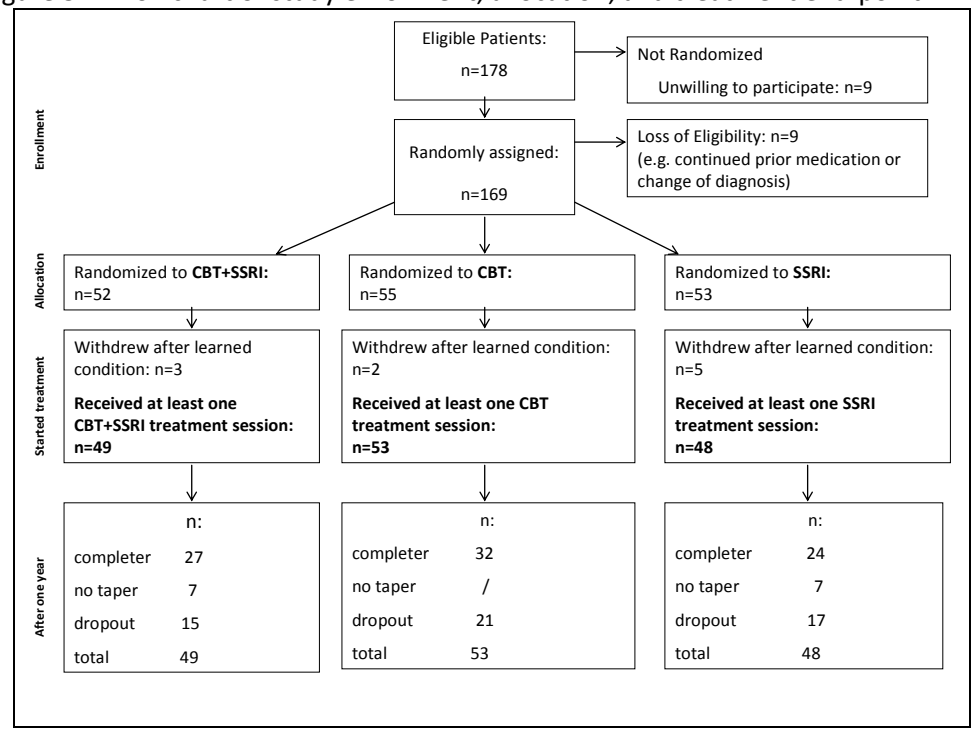
Sample information

After screening and randomization, 150 patients started treatment (see Figure 5.1 for flowchart). According to our definition, 83 out of 150 patients who started treatment were completers of which CBT+SSRI: n= 27, CBT: n=32, SSRI: n=24 (total n=83). In the completer sample, 56.6% was female. Mean age was 36.6 years (SD 10.7). On average, patients had suffered from PD for 7.4 (SD 7.9) years at pretest. About half of the patients in the completer sample did not suffer from AG or suffered from only mild AG (48.2%, n=40 of which n=7 no AG, and n=33 mild) while the other half suffered from moderate or severe AG (51.8%, n=43 of which n=32 moderate, and n=11 severe).

CBT completers received a mean of 19.0 (SD 4.0, range 7-25)[5] sessions. SSRI completers received a mean of 11.6 (SD 1.3, range 9-15) sessions. CBT+SSRI completers received a mean of 18.6 (SD 3.01, range 11-22) CBT sessions and a mean of 11.8 (SD 1.3, range 9-14) SSRI sessions.

[5] In four CBT-only cases, therapist and patient both agreed that more treatment sessions were not applicable because of early treatment success. These CBT completer patients received less than 15 CBT sessions (7, 11, 12 and 14 CBT sessions respectively).

Figure 5.1. Flowchart of study enrollment, allocation, and treatment end-point



Rate of improvement

Parameter estimates of Model I are presented in Table 5.2. As can be seen in Table 5.2 and Figure 5.2, patients in all three treatment modalities improved significantly (effect of Week and Lnweek) on the frequency of panic attacks during treatment. As can be seen in Figure 5.2, the expected frequency of panic attacks declined fastest after starting treatment and then levels off, resulting in virtually no panic attacks at all by the end of the year.

Table 5.2. Estimated coefficients and standard errors of the multilevel poisson models

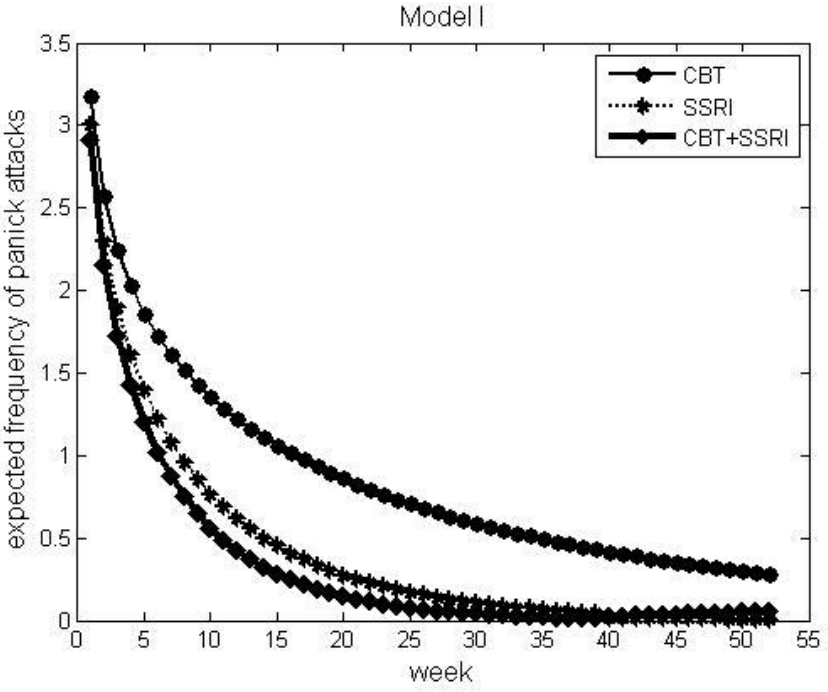
	Model I		Model II	
Fixed effects:	Estimate	S.E.	Estimate	S.E.
Intercept	1.18*	0.16	1.20*	0.23
Week	-0.03*	0.00	-0.04*	0.01
Lnweek	-0.27*	0.05	-0.27*	0.05
Week*SSRI	-0.06*	0.01	-0.06*	0.01
Week* CBT+SSRI	-0.09*	0.01	-0.05*	0.01
Dweek40*SSRI	-4.45	27.82		
Dweek40* CBT+SSRI	-29.64	17.62		
Dweek40*SSRI*Lnweek	0.97	7.32		
Dweek40*CBT+SSRI*Lnweek	8.25	4.61		
AG status			-0.03	0.31
AG status * Week			0.02*	0.01
AG status * Week * SSRI			0.00	0.01
AG status * Week * CBT+SSRI			-0.05*	0.01
Random effects:				
Intercept	1.18*	0.16	1.69*	0.29

Note: NA = Not Applicable, S.E.= Standard Error, * $p<0.05$

Treatment differences in rate of improvement

Model I revealed that the number of panic attacks in both SSRI and CBT+SSRI dropped significantly faster in time as compared to CBT (as indicated in Table 5.2 by the significant interactions between Week and SSRI, and Week and CBT+SSRI, respectively), whereas the difference in rate of improvement between SSRI and CBT+SSRI appeared to be non-significant (not shown explicitly in Table 5.2).

Figure 5.2. Plot of expected frequency of panic attacks according to Model I for three groups: CBT, SSRI, and CBT+SSRI



Additional analyses per week revealed significant differences in panic frequency between treatment groups at weeks 6,7,10,11,27-31,33-37 and week 40 (all $p \leq .03$). Subsequent pair wise analyses revealed that in all these weeks CBT was outperformed by SSRI (weeks 11 and 33), or by CBT+SSRI (weeks 6 and 29), or by both CBT+SSRI and SSRI (the remaining weeks).

The effect of tapering medication on frequency of panic attacks

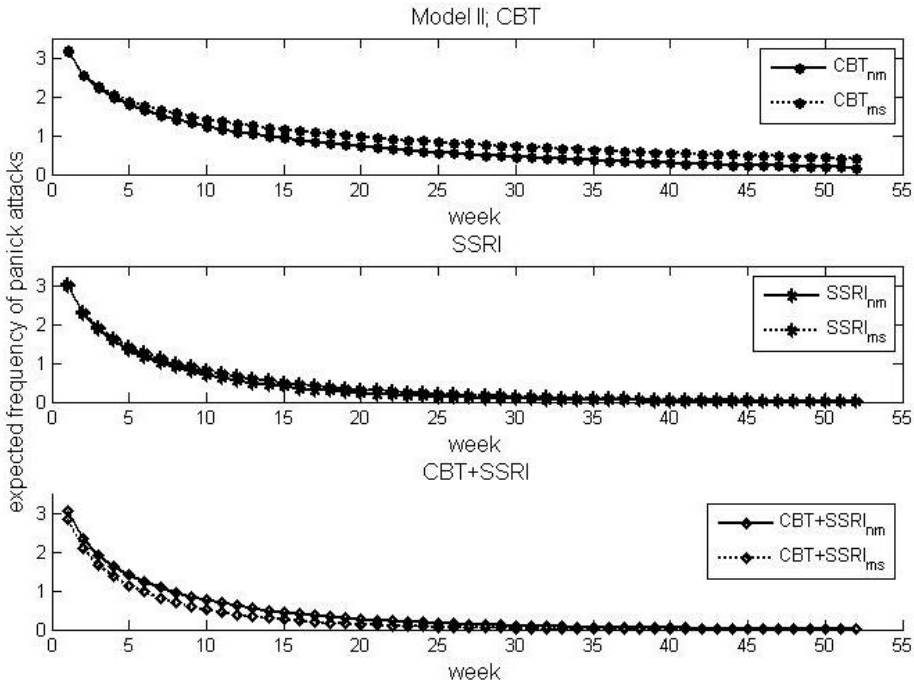
From week 40, patients receiving an SSRI started to taper medication. For CBT+SSRI and SSRI, Model I revealed no significant changes in panic attack frequency from

week 40 (start tapering) up to week 52 (tapering completed) (indicated by non-significant two-way interaction effects of Dweek40 by SSRI and CBT+SSRI, respectively) implying that gains were maintained throughout medication taper. Also, no differential effects between SSRI and CBT+SSRI were found from week 40 up to week 52 (indicated by non-significant three-way interaction effects of Dweek40 and Lnweek by SSRI and CBT+SSRI, respectively).

The relationship between rate of improvement and baseline severity of agoraphobia

The parameter estimates of Model II are also presented in Table 5.2. The expected frequencies, on the basis of Model II, as a function of week and AG status (no/mild vs. moderate/severe) are depicted in Figure 5.3, for each treatment modality separately. As can be seen in Table 5.2, no significant main effect of AG status (no/mild vs. moderate/severe) was found indicating that the frequency of reported panic attacks appeared to be equal at week 0 among patients with moderate or severe AG and patients without of with only mild AG. We subsequently found a positive significant interaction effect of AG status with week (effect of AG status * Week) and no differential effect of SSRI (effect of AG status * Week * SSRI), suggesting that patients in the SSRI and CBT condition with moderate/severe AG showed less decrease in reported panic attacks during treatment as compared to patients with no/mild AG. Subsequently, we also found a negative significant interaction effect of AG status, week, and CBT+SSRI (effect of AG status * Week * CBT+SSRI), indicating that among patients with moderate or severe AG, rate of improvement was faster with CBT+SSRI as compared to SSRI and CBT.

Figure 5.3. Plot of expected frequency of panic attacks according to Model for CBT (nm/ms), SSRI (nm/ms), and CBT+SSRI (nm/ms) in which nm = no AG or mild AG and ms = moderate or severe AG



DISCUSSION

To our knowledge, this is the first study to analyze the differential rate of improvement in panic frequency in a randomized trial evaluating CBT, SSRI and the combination of both for PD with or without AG. As expected, randomized patients who completed treatment showed a decline in number of panic attacks during treatment, resulting in virtually no panic attacks at the end of treatment. Thus, all three treatments tended to lead to improvement on the key symptom of PD, namely

panic attacks. Although it was expected that patients who received CBT would need more time to reach the same rate of improvement as patients who were assigned to SSRI and CBT+SSRI, we were surprised to find that patients who received CBT reported relatively more panic attacks not only in the first phase of treatment but throughout the entire year. Furthermore, the difference in frequency of panic attacks reached statistical significance even up to week 40. A treatment with SSRI-only appeared equally effective in diminishing the frequency of panic attacks as the combined treatment implying that no additive value of CBT to SSRI-only was observed.

Clinical studies reveal that SSRIs need about four to six weeks of treatment before becoming effective.[21] Visual inspection of Figure 5.2 suggests that frequency of panic attacks started to decline from week 1 in each treatment modality. Subsequent analyses revealed that there were no significant differences between treatment modalities up to week 6 suggesting that SSRIs indeed started to become effective from week 6, resulting in significant differences in weeks 6-12, while CBT treatment needed more time to become equally effective. This would be in agreement with current understanding of the neurobiology of PD.[22] It is thought that CBT and SSRI may operate through different pathways in the brain leading to a different pattern of response over time. Following this, it might be expected that when using an SSRI, effects will first be observed on the level of somatic symptoms resulting in a more rapid decline of panic attacks as compared to CBT. It could be presumed that CBT would reveal its therapeutic effect in the early phase of treatment on different process measures (e.g. belief in catastrophic cognitions) but up to date, no data is available to corroborate this.

Regarding the context-safety hypothesis, we found no evidence for the assumption that patients having discontinued the SSRI subsequently relapse due to a

shift in context. In the ten weeks following tapering medication, patients in SSRI and CBT+SSRI maintained achieved gains regarding panic frequency. It can be argued that for patients receiving both CBT and SSRI, CBT enhances patient's confidence in coping with possible withdrawal effects during tapering. Interestingly however, patients receiving SSRI-only also maintained their gains following medication taper, questioning the additive value of CBT. Possibly, the adequate information and guidance of clinicians through-out the tapering process contributed to the prevention of relapse but more research is clearly needed on relapse factors.

Present findings support the notion that patients with PD and moderate or severe AG at baseline are more seriously impaired in daily functioning as compared to patients with PD without AG.[15] Although it is suggested that there is no reason to offer PD patients with AG a different kind of treatment than patients without AG,[16] present findings suggest that specifically for patients with moderate to severe AG, a combined CBT and SSRI treatment offers a surplus value to both monotreatments. This is in line with the notion that especially exposure-based techniques are considered to be important in the treatment of moderate to severe AG.

Strengths of the present study include the advanced statistical techniques applied, which resulted in a sound model of rate of improvement in panic frequency during and across the different treatment modalities. Also, results can be considered highly externally valid with respect to type of patients, type of treatments, and type of treatment centers[6] which allows practitioners to draw inferences regarding clinical practice.

The fact that frequency of panic attacks was not assessed beyond the full year of treatment can be considered a limitation of this study. Panic frequency data was collected for one year (albeit long as compared to other studies), until ten weeks following medication taper. We cannot rule out the possibility that relapse occurred

in the weeks after that, although follow-up assessments, six and twelve months after medication taper, again revealed no relapse on several outcome measures.[5] A second factor that possibly limits the reliability of our findings is the fact that patients' compliance to accurate and immediate completing the panic plot is not assessed in this study. However, every session the panic plots were checked upon receipt for the accuracy of completion by the therapist. In general, event-contingent recording have been particularly suitable for data collection in the domain of psychopathology, when the clinical symptoms are sudden and have acute onset.[23] A third limitation is that we did not collect another process variable, next to panic frequency, to supplement present findings. Although irrefutable a core symptom of PD, other important aspects of the disorder would have been interesting regarding rate of improvement as well. A suggestion for future research might be adapting a more process-oriented approach in which timing and sequencing of changes regarding different aspects of PD within and across treatments is the focus (for examples of such a process-oriented approach, see[24,25]). This might lead to a better understanding of processes involved in recovery from PD as a result from different treatment modalities.

In the treatment guidelines for PD we have seen a development from a more psychopharmacological approach to a more psychological approach. What can we suggest the practitioner facing the decision how to treat his PD patients, based on present findings? From a cost-effectiveness perspective, SSRI seems first choice because it results in a rapid decline in the number of panic attacks and leads to no relapse following medication taper. For patients with moderate or severe AG however, the combined CBT+SSRI treatment may be recommended because for this patient group, a combined package was associated with the most rapid decline in the number of panic attacks and again, no relapse after medication taper was observed.

The latter finding is especially important considering the hesitancy that clinicians tend to feel towards tapering, which can result in ongoing, perhaps even unnecessary, SSRI treatment.

We emphasize the need to integrate insights from contemporary learning theory in clinical studies under real life conditions with real life PD patients. The present study contributes to this endeavor as no stringent inclusion criteria were applied, clinical practice sites joined and treatments were delivered according to care as usual. In this way, we may come to understand how phenomena observed in the laboratory (such as context dependency in the extinction of fear), emerge into the clinical practice of treating PD patients. Future studies are required to examine the effects of SSRI, CBT, and CBT+SSRI on other process measures than frequency of panic attacks to validate our findings.

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CHAPTER 6

COST-EFFECTIVENESS

This chapter is a slightly altered version of a previous publication:
Cost-effectiveness of CBT, SSRI, and CBT+SSRI in the treatment for panic disorder.
Franske J. van Apeldoorn, A. Dennis Stant, Wiljo J.P.J. van Hout,
Peter Paul A. Mersch, Johan A. den Boer (2013).
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ABSTRACT

Knowledge about the cost-effectiveness of different treatment modalities can support providers in optimally allocating scarce resources. The objective of the present study was therefore to assess the cost-effectiveness of three empirically supported treatments for PD with or without AG: CBT, SSRI, or the combination of both. Cost-effectiveness was examined based on data from a multicenter randomized controlled trial. The Hamilton Anxiety Rating Scale was selected as primary health outcome measure. Data on costs from a societal perspective (i.e. direct medical, direct nonmedical and indirect nonmedical costs) was collected in the study sample (n=150) throughout a 24-month period in which patients received active treatment during the first twelve months and were seen twice for follow-up in the next twelve months. Results showed that total costs were largely influenced by costs of the interventions and productivity losses. The mean total societal costs were lower for CBT as compared to SSRI and CBT+SSRI. Costs of medication use were substantial for both SSRI and CBT+SSRI. When examining the balance between costs and health outcomes, both CBT and CBT+SSRI led to more positive outcomes than SSRI. It was concluded that CBT is associated with the lowest societal costs and that CBT and CBT+SSRI are more cost-effective treatments for PD with or without AG as compared to SSRI-only.

INTRODUCTION

Panic disorder (PD) is a disabling condition associated with reduced quality of life[1] and impaired functioning. In cases of additional severe agoraphobia (AG), PD can result in being completely housebound. Costs associated with PD thus not only include direct medical costs but also indirect costs resulting for instance from reduced productivity.[2] In this way, PD imposes a burden on both health care systems and society as a whole. It is estimated that for PD, costs per patient per year surpass the costs of depressive disorder.[3] The need for economic evaluations of treatments for mental illnesses stems from the current context of managed care characterized by accountability and cost containment.[4] Economic evaluations focus on the balance between costs and health outcomes (i.e. treatment outcome measures) of alternative interventions in the field of healthcare. In conducting these evaluations, data on both direct and indirect costs need to be collected.[5] Knowledge about the cost-effectiveness of different treatment modalities can support providers in optimally allocating scarce resources.

Empirically supported treatments for PD include both cognitive behavioral, pharmacologic, and combined treatments. Numerous studies have demonstrated the effectiveness of both monotreatments but scientific interest in the combined treatment is from a more recent date and important questions regarding long-term effectiveness and relapse after treatment discontinuation await further investigation. Some studies suggest a detrimental effect of combined treatments on the long-term.[6] Tapering medication following successfully treating PD patients with both CBT and pharmacotherapy would lead to relapse. One of the explanations for relapse might be a shift in context: what is learned within the context of medication-use might not be preserved in a non-medication context.[7] Following this line of

reasoning, it might be assumed that on the long-term (i.e. after completing treatment), a combined treatment is associated with higher costs as compared to monotreatments. Regarding monotreatments; while pharmacotherapy is generally associated with more relapse,[8,9] CBT-only is characterized as durable on the long-term,[10] and especially cost effective with patients needing no additional treatment after successfully completing therapy.

It must be noted however that these considerations are largely based on experimental- and treatment outcome data rather than on cost-effectiveness data. In fact, studies evaluating costs associated with these treatments are scarce[4] and drawing conclusions is hampered by methodological differences between studies.[2] Specifically, there is a need for comparing costs of different treatment modalities within a single design. One such study is the multi-site randomized trial comparing imipramine, CBT, and their combination for PD.[6] In the economic evaluation of these data, monotreatments proved to be associated with greater cost-efficacy as compared to the combined treatment. After three months, imipramine was the most cost-efficacious treatment and six and nine months after treatment termination, this was the case for CBT.[4] It is important to note that only direct costs were assessed in this study. No studies on PD to date have examined the cost-effectiveness of direct and indirect costs (e.g., productivity loss) of the combined CBT+SSRI treatment compared to both monotherapies within a single design. In the present study data from our randomized controlled trial comparing three empirically supported treatments[11] were used in an economic evaluation from a societal perspective.

The aim of the present study is to determine the most cost-effective treatment for panic disorder with or without agoraphobia in an economic evaluation from a societal perspective comparing Cognitive Behavioral Therapy, pharmacotherapy using a Selective Serotonin Reuptake Inhibitor, or the combination of both.

METHOD

Study participants, treatment modalities and study design

Randomized patients suffered from a primary diagnosis of PD with or without AG. Patients were randomized to receive CBT, SSRI, or CBT+SSRI. During the first treatment year, CBT patients received up to 21 treatment sessions (50 minutes each) in 52 weeks. The CBT treatment manual was intended to satisfy as closely as possible "care as usual" requirements and was based on the work of Clark, Craske, and Barlow.[12,13] Patients receiving an SSRI visited their therapist 9 times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. For patients randomized to CBT+SSRI, the two treatments started simultaneously and were delivered parallel by two different therapists.

The economic analyses focused on the 24 months consisting of twelve months active treatment and twelve months follow-up period. Costs and health outcomes were assessed prospectively for all the included patients. Patients were assessed five times; before starting treatment (T0), after nine months of treatment (before starting medication taper) (T9), at treatment endpoint (after medication taper) (T12), six months after treatment termination (T18), and twelve months after treatment termination (T24), resulting in four measurement periods: T0-T9, T9-T12, T12-T18, T18-T24.

Costs and unit prices

The study was conducted from a societal perspective; direct medical, direct nonmedical and indirect nonmedical costs were registered. Direct medical costs included costs related to the interventions (CBT, SSRI, CBT+SSRI), inpatient and semi-inpatient care, outpatient and community care, general healthcare, day activity institutions, and medication. Direct nonmedical costs included time costs and informal care. Informal care refers to care provided by caregivers such as neighbors or family. Indirect nonmedical costs included costs of productivity losses due to illness-related absence from paid work.

Costs of the interventions were based on the number of visits for medication management and or CBT treatment sessions, the wages of psychiatrists and or therapists, and additional costs (e.g. costs of housing). Costs of informal care were based on the monetary valuation of the time invested by informal caregivers in helping or assisting the patient. Medication use, including medication other than SSRI according to protocol, was registered in detail for all the included patients. Costs of productivity losses due to illness-related absence from work were estimated by means of the friction cost method.[15] Compensation mechanisms were taken into account when estimating productivity costs, in accordance with the methods described by Jacob-Tacken and colleagues.[16]

Most data was collected by means of a detailed questionnaire on costs administered by trained research assistants in a face-to-face interview with study participants. This interview was conducted five times and thus focused on the four measurement periods: T0-T9, T9-T12, T12-T18, T18-T24. The interview assessed, among others, admissions to psychiatric hospitals, contacts with healthcare professionals, and absence from work. Additional information was collected through

healthcare professionals involved, for instance on the use of (prescribed and non-prescribed) medication.

In order to facilitate comparisons with other economic evaluations, unit prices, i.e. the price of one unit of each included cost type, were mainly based on Dutch standard prices.[17] True costs of used resources were estimated when standard prices were not available. All unit prices were based on the price level of the Euro in the year 2005. Reference prices established for previous years were adjusted to prices of 2005 by applying the consumer price index.

Cost-effectiveness analysis

In cost-effectiveness analysis, costs and the primary health outcome associated with an intervention are used to calculate the incremental cost-effectiveness ratio (ICER) relative to one or more alternatives.[18] In the present study, the Hamilton Anxiety Rating Scale (HAM-A)[19] was selected as the primary health outcome measure for the cost-effectiveness analysis. This instrument is well-validated and widely used in studies aimed at anxiety disorders. The power analysis was based on characteristics of the HAM-A in the patient population under study. Previous analyses focusing on the HAM-A demonstrated that differences between groups were not statistically significant when focusing on the full 24 months of the study. Additional details on the results on effectiveness using the HAM-A as health outcome measure are presented elsewhere.[11] In the present study, we will present the cost-effectiveness results only. ICERs were calculated using the mean changes in HAM-A scores over time and societal costs of the three groups during the 24 months of the study.

The formula for calculating the ICER is presented below (only displayed for the comparison between the CBT and SSRI group):

$$ICER = \frac{(C_{CBT} - C_{SSRI})}{(\text{HAM-A}_{CBT} - \text{HAM-A}_{SSRI})}$$

C_{CBT} = mean costs in the CBT group
C_{SSRI} = mean costs in the SSRI group
HAM-A_{CBT} = mean HAM-A difference score in the CBT group
HAM-A_{SSRI} = mean HAM-A difference score in the SSRI group

The bootstrap method was applied to provide information on the uncertainty of the results of the economic evaluation. Bootstrapping[20] is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. ICERs were calculated for each of the bootstrap iterations (5000 in the present study). Simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness plane.[21] Subsequently, cost-effectiveness acceptability curves (CEACs)[22] were calculated. CEACs inform decision-makers on the probability that an intervention will be cost-effective, which depends on the willingness to pay per additional unit of health outcome.

Finally, two sensitivity analyses were conducted in order to provide information on the robustness of the results of the economic evaluation. There are currently several methodological approaches towards the measurement of productivity losses available, and estimates of these costs may vary considerably between approaches. In the first sensitivity analysis, costs of productivity losses were therefore excluded, which was also expected to simplify direct comparisons with previous economic

studies in which costs of productivity losses could often not be registered.

Patients were followed for 24 months and various measurements were scheduled during this time frame. Before the start of the study, it was anticipated that some patients might drop out of the study, or data might not be available for all patients at one or more of the measurements. Therefore, in a second sensitivity analysis an imputation technique (see also the section on statistical analysis) was applied as an alternative for the complete case approach in the standard cost-effectiveness analysis.

Statistical analysis

All analyses were conducted in agreement with the intention-to-treat (ITT) principle implying that participants were analyzed in the condition to which they were randomized. We have no data from patients who refused to participate and withdrew from the study before the first assessment; these patients were not included in the ITT analysis.

The significance of differences in mean total costs between groups was analyzed by 95% confidence intervals estimated with the bootstrap method for available cases per measurement, and complete cases over the 24 months of the study. In one of the sensitivity analyses, missing cost data were imputed with the expectation maximization (EM) algorithm. The EM algorithm consists of an iterative process, estimating values for missing data based on the observed data[23]

RESULTS

Study sample

One hundred and seventy-eight eligible subjects were seen for screening. Nine subjects were unwilling to participate. One hundred and sixty nine subjects were randomized to treatment of which nine lost eligibility prior to starting treatment. Also, ten subjects withdrew from the study after they were told to which treatment they were randomized and before any assessment was conducted. Subsequently, 150 patients started treatment of which CBT+SSRI: n = 49, CBT: n = 53, and SSRI: n = 48. In total, 54.7% of the sample consisted of women. Mean age was 37.5 years (range 18–61 years). About half of the patients in the present sample did not suffer from AG or suffered from only mild AG (48%) while the other half suffered from moderate or severe AG (52%).

Cost types and healthcare utilization

The various medical and nonmedical costs generated by each patient group during the 24 months of the study are depicted in Table 6.1. Furthermore, Table 6.1 also displays information on the utilization of healthcare services as the percentage of patients using each cost type is provided.

Table 6.1. Mean medical and nonmedical costs (in euro) for participants in three treatment groups during 24 months

	CBT (n=52)		SSRI (n=47)		CBT+SSRI (n=49)	
Cost types	mean costs (SD)	%[1]	mean costs (SD)	%[1]	mean costs (SD)	%[1]
Interventions:						
Therapy/contacts	690 (308)	98	257 (125)	89	924 (406)	92
Medication:						
Prescribed	25 (154)	4	348 (326)	81	433 (449)	82
Nonprescribed	52 (342)	19	27 (107)	15	22 (117)	18
Inpatient and semi-inpatient care:						
Hospital admission	0 (-)	0	0 (-)	0	0 (-)	0
Day care	0 (-)	0	8 (56)	2	0 (-)	0
Sheltered accommodation	0 (-)	0	0 (-)	0	0 (-)	0
Outpatient and community care:						
Psychiatrist	5 (25)	4	21 (69)	15	52 (153)	20
Psychologist	185 (453)	21	75 (219)	15	182 (512)	27
Social psychiatric nurse	0 (-)	0	0 (-)	0	0 (-)	0
Social worker	0 (-)	0	0 (-)	0	0 (-)	0
Crisis intervention	0 (-)	0	5 (31)	2	0 (-)	0
Psychiatric homecare	0 (-)	0	0 (-)	0	0 (-)	0
CAD[2]	0 (-)	0	0 (-)	0	0 (-)	0
Other outpatient care	47 (332)	4	51 (185)	11	1 (7)	2
General healthcare:						
General practitioner	19 (58)	19	25 (78)	26	6 (20)	14
Alternative healthcare	13 (89)	4	6 (23)	9	9 (47)	6
Home care	0 (-)	0	0 (-)	0	21 (145)	2
Emergency care	0 (-)	0	3 (21)	2	0 (-)	0
Other general healthcare	46 (162)	12	21 (80)	9	17 (53)	12
Day activity institutions:						
Day activity center	0 (-)	0	0 (-)	0	0 (-)	0
Drop-in center	0 (-)	0	0 (-)	0	0 (-)	0
Other institutions	0 (-)	0	0 (-)	0	0 (-)	0
Nonmedical costs:						
Time costs	110 (49)	98	26 (13)	89	133 (58)	92
Informal care	91 (541)	6	393 (1496)	15	72 (248)	8
Productivity losses	776 (2284)	13	1136 (2576)	26	1068 (2337)	24

Medical costs directly related to the three interventions ranged from €257 for SSRI-only, to €924 for the combination of CBT and SSRI. For CBT-only, mean costs of medication use were, as expected, considerably lower than in the other treatment modalities.

No patients were admitted to a hospital or stayed in a sheltered accommodation during the study. Of the various types of outpatient services, by far the most care was provided by psychologists. Approximately 20% of the patients visited their general practitioner at least once. Time costs directly related to the interventions were lower for SSRI as compared to CBT and CBT+SSRI. Patients in the SSRI group seemed to make more use of informal care than the other groups. Costs of productivity losses were substantial in all three groups ranging from €776 for CBT to €1136 for SSRI.

Total costs

An overview of the mean total costs generated during the various measurement periods of the study is provided in Table 6.2. In addition, the number of patients available at each measurement is presented.

Costs were highest during the first twelve months of the study, which was related to the interventions that were provided during this period, the more intensive use of healthcare services, and the temporary increase in illness-related absence from work.

Table 6.2. Costs (in euro) for three treatment groups during 24 months and the 95% CI of mean differences between groups

	CBT		SSRI		CBT+SSRI	
	n	Mean total costs	n	Mean total costs	n	Mean total costs
Measurement period						
T0-T9	52	1501	46	1904	49	1746
T9-T12	51	403	45	202	48	596
T12-T18	33	114	30	363	35	603
T18-T24	34	140	27	196	33	266
T0-T24 [1]	32	2224	27	3118	32	3590

95% CI [2]	*LB*	*UB*
CBT versus SSRI	-3315	1071
CBT+SSRI versus SSRI	-2182	2171
CBT+SSRI versus CBT	-225	2481

[1] Mean total costs during T0-T24, based on data of participants for whom all the relevant measurements were available (complete cases)

[2] 95% confidence interval (CI) for the mean cost differences between the various groups during T0-T24, based on complete cases. Lower (LB) and upper boundaries (UB) of the CI are presented

Mean total costs during the 24 months of the study were €2224 for CBT, €3118 for SSRI, and €3590 for CBT+SSRI. Costs associated with the CBT-only group appeared to be considerably lower than in the other groups. However, differences between the mean total costs were not statistically significant, as indicated by the boundaries of the 95% confidence intervals assessed with the bootstrap method. The absence of significant differences between costs of the three groups should be interpreted with some caution, since the study was powered (as most economic evaluations) to demonstrate differences in health outcomes and not costs.

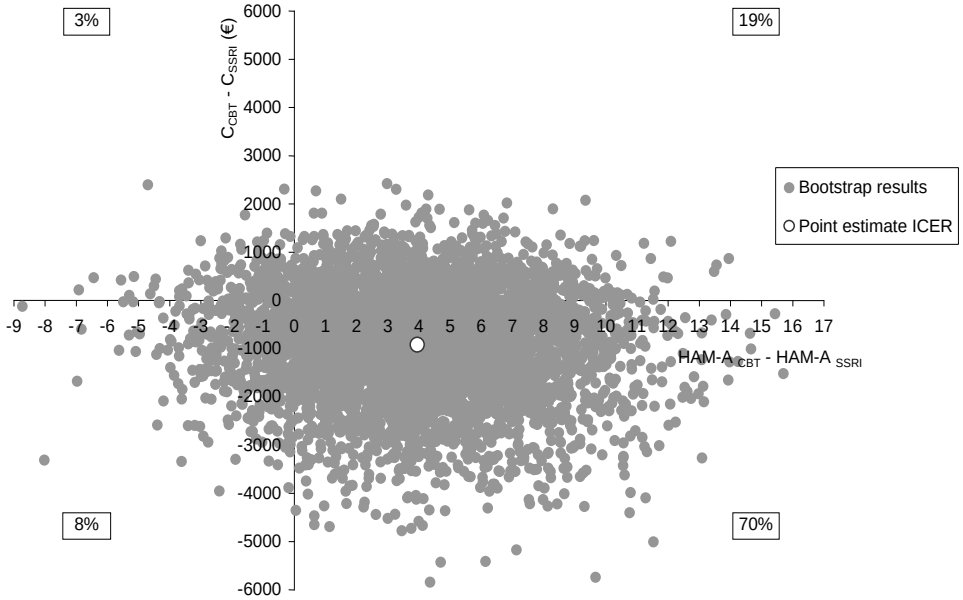
Cost-effectiveness analysis

For the current cost-effectiveness analysis, changes in mean HAM-A scores between baseline and the end of follow-up were assessed. The three groups all showed improvements over time (mean HAM-A improvement of 10.6 points in the SSRI group, 14.5 in the CBT group, and 16.2 in the CBT+SSRI group), but differences between groups were not statistically significant (F=1.815, p=.169). For the standard cost-effectiveness analysis only cases with complete data were included. Complete data (on costs and outcome) were available for 32 CBT patients (60% of the patients who started CBT treatment). For the SSRI group, complete data were available for 27 patients (56% of the patients who started SSRI treatment). For the CBT+SSRI group, complete data were available for 32 patients (65% of the patients who started CBT+SSRI treatment).

The point estimate of the ICER and the results of the bootstrap analyses are presented in the cost-effectiveness planes (CEPs) in Figures 6.1 A/B/C. Furthermore, information is provided on the percentage of bootstrap simulations located in each quadrant of the CEPs.

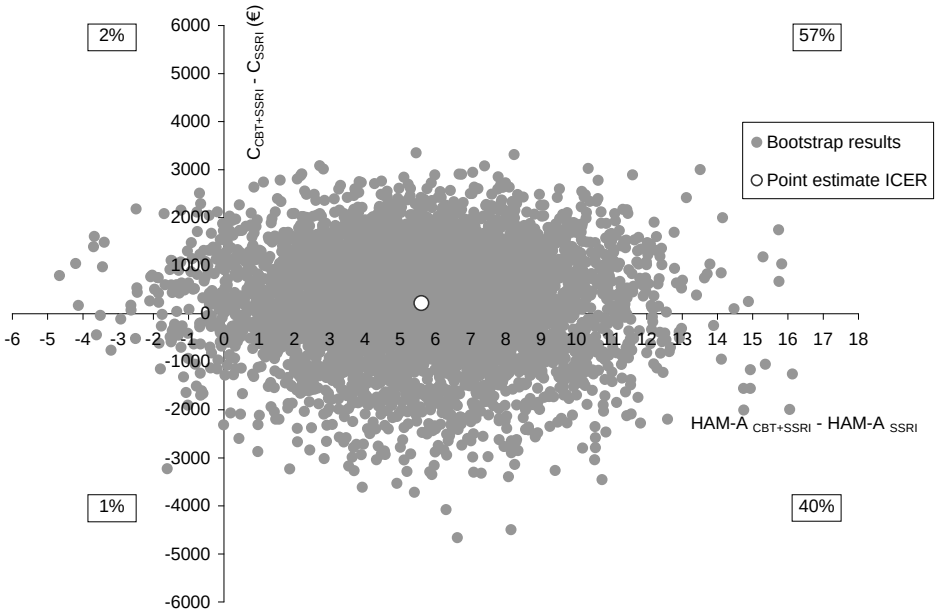
Figure 6.1. Results of the cost-effectiveness analyses and bootstrap method

6.1A CBT compared to SSRI:



For the comparison between CBT and SSRI (see Figure 6.1A), the point estimate and approximately 70 % of the bootstrap simulations is located in the southeast quadrant. In other words, CBT dominated SSRI in 70% of the simulations implying lower costs and better health outcomes for CBT as compared to SSRI. For the comparison between CBT+SSRI and SSRI (see Figure 6.1B), the point estimate is located in the northeast quadrant, i.e. mean costs were higher but health outcomes were better in the CBT+SSRI group as compared to SSRI. Furthermore, CBT+SSRI dominated SSRI in 40% of the cases.

6.1B CBT+SSRI compared to SSRI



Finally, a direct comparison was made between CBT+SSRI and CBT (see Figure 6.1C). CBT+SSRI was associated with higher costs but better health outcomes as compared to CBT. By far the most bootstrap outcomes are located in the northeast quadrant. Interpretation of outcomes in the northeast (and southwest) quadrant depends on how much decision-makers are willing to pay for an additional unit of health outcome.

6.1C CBT+SSRI compared to CBT

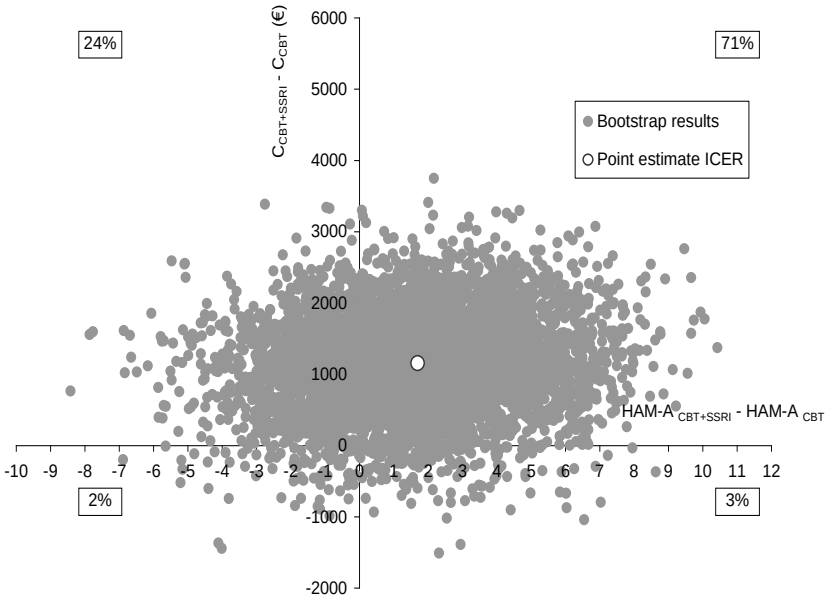
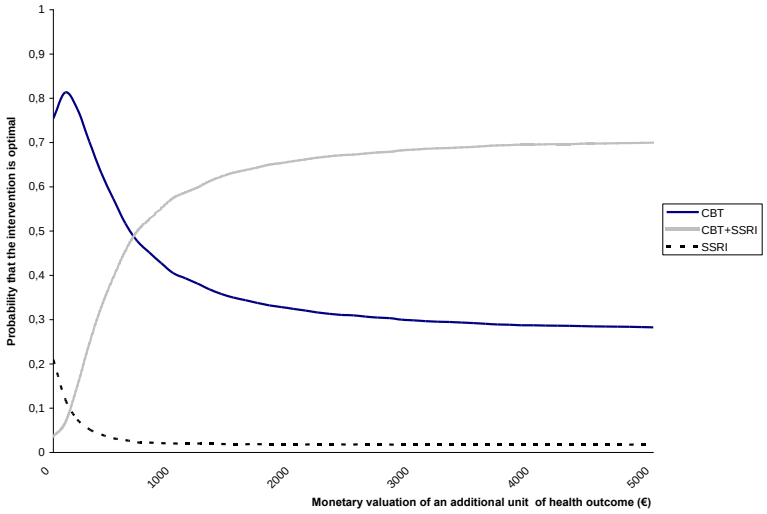


Figure 6.2 shows the probability that the interventions will be cost-effective for increasing willingness to pay per additional unit of health outcome. CBT is preferred over CBT+SSRI if the willingness to pay is lower than approximately €700 per additional point on the HAM-A. When decision-makers are willing to pay more than this amount, CBT+SSRI is more likely to be cost-effective than CBT.

Figure 6.2. Cost-effectiveness acceptability curves



Sensitivity analysis

Results of the two sensitivity analyses are presented in Table 6.3.

Table 6.3. Sensitivity analyses

Type of analysis	CBT mean total costs (SD)	SSRI mean total costs (SD)	CBT+SSRI mean total costs (SD)
Type of analysis:			
Exclusion of productivity costs	1625 (1354)	1804 (2181)	2271 (1132)
Imputation missing cost data[1]	2271 (3062)	2591 (3914)	3159 (3012)

[1] Imputation with the EM algorithm to account for missing cost data. Mean costs are based on the data of 52 CBT, 47 SSRI, and 49 CBT+SSRI patients.

The exclusion of costs related to productivity losses was associated with much lower costs in all three groups, and resulted in smaller differences between groups. When excluding costs of productivity losses, mean total costs were €1625 for CBT, €1804 for SSRI, and €2271 for CBT+SSRI.

In the second sensitivity analysis, missing cost data were imputed by means of the EM algorithm. Cost outcomes were again in favor of the CBT group, but differences with the other groups were smaller than in the standard analyses.

DISCUSSION

To our knowledge, this is the first economic evaluation of the treatment of PD with or without agoraphobia in which SSRI, CBT, and the combination of both are directly compared within the same design. Although differences in costs and health outcomes between groups did not reach statistical significance when focusing on the 24 months of the study, the presented results seem highly relevant for policy decisions in mental healthcare. Nowadays, there appears to be wide consensus that the focus of economic studies should actually be on estimation and the assessment of probability (of the relative cost-effectiveness of healthcare interventions), instead of hypothesis testing.[25,26] In the present study, the uncertainty surrounding the current economic results was, among others, assessed by means of bootstrap techniques and graphically presented by cost-effectiveness acceptability curves. The provided information on the relative cost-effectiveness of CBT, SSRI, and CBT+SSRI (together with the uncertainty of the outcomes) could be used by decision-makers to re-allocate the limited resources within healthcare, and eventually optimize the treatment of PD in current healthcare systems.

In all three groups, total costs were largely influenced by costs of the

interventions and productivity losses. Furthermore, costs of medication use were substantial for patients in both the SSRI and CBT+SSRI group. When examining the balance between costs and health outcomes, both CBT and CBT+SSRI led to more positive outcomes than SSRI-only. Although CBT was associated with lower costs, assessed health outcomes were slightly more in favor of CBT+SSRI. Which of these two interventions is to be preferred depends on the decision-makers' willingness to pay. When decision-makers are willing to pay less than €700 (€0 - €700) per additional point on the HAM-A, CBT is likely to be the most optimal intervention from a cost-effective perspective. When the willingness to pay exceeds €700 per additional point on the HAM-A, CBT+SSRI has the highest probability of being the most optimal intervention.

It is important to keep in mind that patients receiving CBT+SSRI and SSRI, tapered medication at the end of the first year and were thus not using an SSRI during the second year of the study. Direct costs of the intervention were, as expected, higher for the combined CBT+SSRI treatment as compared to intervention costs of the monotherapies. However, on the long term, CBT+SSRI proved to be more cost-effective than SSRI-only. Our data revealed no long-term detrimental effect of the combined treatment as was suggested by others.[6]

While the present cost-effectiveness analysis shows that CBT+SSRI and CBT are more cost-effective treatment modalities as compared to SSRI-only, results of the study by Mc Hugh et al., suggest monotherapies to be more cost-efficacious as compared to combined treatment.[4] However, this study differs from the present study on several methodological aspects. The Mc Hugh et al. study is presented as an efficacy study rather as an effectiveness study due to the fact that treatments were delivered in specialized treatment centers under best conditions possible. The present study on the other hand, aimed at delivering treatments in real-practice,

under care as usual conditions, and without stringent inclusion criteria which makes it an effectiveness study rather than an efficacy study.[27,28] Further, patients receiving pharmacotherapy received imipramine rather than an SSRI while the latter is considered first-line pharmacological treatment for PD. Also, only patients without AG were included while in the present sample, half of the subjects suffered from moderate to severe AG. Finally, only direct costs were assessed in the McHugh et al. study thereby not addressing the issue of considerable indirect costs associated with PD.

Limitations of the present study include the fact that only complete cases were included although this was obviated by conducting an additional sensitivity analysis focusing on imputation of missing data which revealed similar overall results. Further, in contrast to several previous studies on the subject of cost-effectiveness in the field of anxiety disorders,[2] QALYs (Quality-Adjusted Life Years) were not assessed in the current study. QALYs may, at least in theory, be used by decision makers to prioritize alternative healthcare interventions on a national level. Unfortunately, there is currently no (inter) national consensus on acceptable benchmarks per QALY gained, let alone for disease-specific outcomes like the HAM-A applied in the current study. Decision-makers will eventually have to interpret whether the indicated costs per additional unit of health outcome gained, as found in this study, warrant further implementation of CBT or CBT+SSRI.

Strengths of the present study include the design of the study in which patients were assessed not only while receiving active treatment but also after treatment discontinuation, e.g. after tapering medication in case of SSRI use. The follow-up period of one year provided extensive information on post-treatment course. Also, both direct and indirect costs were included in the analyses. Further, three treatment variants for PD with or without AG were directly compared within a single

cost-effective analysis, which makes optimal use of the data and enhances the interpretability of the current economic results. Finally, this study being an effectiveness study rather than an efficacy study attests to the generalizability of present findings.

In conclusion, the present cost-effectiveness analysis shows that the optimal treatment for PD with or without AG is CBT or CBT+SSI. Future research may attempt to further clarify the relationship between the level of comorbid AG and treatment allocation. The results from chapter 5 which focused on rate of improvement in the same multicenter trial, revealed that especially for PD patients with additional AG, the combined CBT+SSRI treatment was to be recommended over the monotherapies. Hypothetically, combining the results of this study and the present study would nominate CBT+SSRI as first-line treatment for PD patients with moderate or severe AG, and CBT as first-line treatment for PD patients without or with only mild AG. Future studies on this subject might benefit clinicians in the field resulting in a refinement of existing guidelines regarding treatment allocation.

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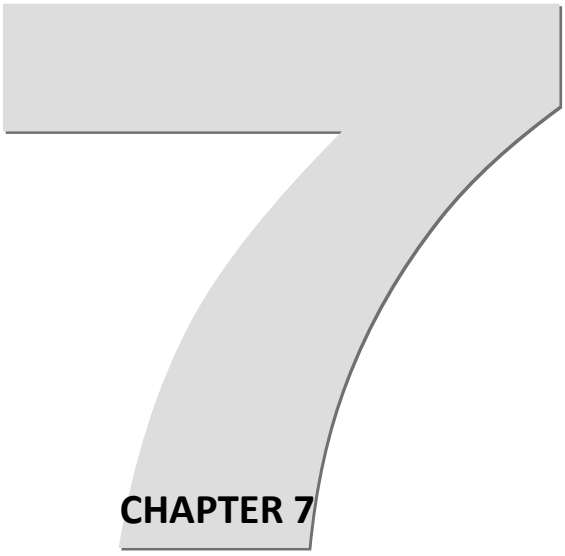

CHAPTER 7

GENERAL DISCUSSION

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7.1 Introduction

The overall goal of the studies in the present thesis was to make a contribution to the on-going search for the best possible treatment for patients suffering from PD with or without AG. To this end, a randomized clinical trial was conducted in the Netherlands comparing CBT, SSRI, and their combination aimed at treating PD with or without AG. Patients were treated for one year including medication taper and subsequently seen twice during the second (follow-up) year of the study. Next to establishing long-term (differential) treatment effectiveness, we aimed at testing the context-safety hypothesis which predicts a detrimental effect of tapering medication. Based on outcome from treatment effectiveness studies, only limited evidence for this hypothesis existed up to date. Additionally, the role of concurrent AG was investigated. Determining differential rate of improvement was also a goal of the present thesis. Finally, we evaluated treatment modalities economically e.g. determined their cost-effectiveness. In the present chapter, the main results of the current thesis will be summarized, points of consideration and clinical recommendations will be discussed, and future directions for research will be proposed.

7.2 Main results

Main results of the current thesis will be summarized and discussed thereby addressing the following topics: treatment effectiveness, differential treatment effectiveness, context-safety hypothesis, role of concurrent AG, rate of improvement, and cost-effectiveness.

Treatment effectiveness

In the present design, patients were assessed before and after tapering, allowing us to directly study the effect of tapering medication. Patients in each treatment group improved significantly from pre- to posttest 1 (see chapter three) on the primary outcome measures level of anxiety, degree of coping, and remitter status, as well as on the secondary outcome measures depressive symptomatology, health related quality of life, and treatment satisfaction. Gains were preserved from posttest 2 through-out the follow-up period. No fall-off in gains was observed for either treatment modality after treatment discontinuation up to the second follow-up (see chapter four).

Differential treatment effectiveness

After nine months of treatment, before starting medication taper (see chapter three), CBT+SSRI was clearly superior to CBT in both completer and intent-to-treat analysis (ITT). Completer analysis revealed superiority of CBT+SSRI over SSRI on three measures and no differences were seen between CBT and SSRI. ITT analysis revealed superiority of SSRI over CBT on four measures and no differences between CBT+SSRI and SSRI. Thus, CBT+SSRI was clearly superior to CBT but differences between CBT+SSRI and SSRI, and between SSRI and CBT, were small. Long-term results were presented in chapter four. Some superiority of CBT+SSRI and SSRI as compared to CBT was observed at posttest 1. However, at both follow-ups, differences between treatment modalities proved non-significant.

These findings match those as reported by De Beurs et al.[(1)] in their naturalistic follow-up study. At posttest, the combined fluvoxamine plus exposure treatment

proved superior to the other treatment modalities (placebo + exposure, psychological panic management + exposure, and exposure alone). Two years after posttest, this superiority was no longer present. It is suggested by the authors that this is not caused by a recurrence of symptoms in the exposure + fluvoxamine group but rather by the other treatment groups catching up during the follow-up period. These findings are in line with a review study on multiple disorders comparing combined CBT and pharmacotherapy with CBT and placebo. Four trials on PD were included. A median post-acute treatment effect was observed and no differences were found between treatment modalities at 6-month follow-up.[2]

It must be noted that in most treatment outcome studies, short term effectiveness is usually assessed within three months after starting treatment (see Table 1.1, chapter one). In a meta-analysis including 21 studies,[3] the typical length of the acute-phase active treatment was between 8 and 12 weeks. In the present thesis, the first assessment took place after nine months and this enables us to evaluate treatments as maintenance therapy. At that time, patients in all groups were significantly improved and CBT+SSRI outperformed CBT-only.

Context- safety hypothesis

Based on the context-safety hypothesis (see chapter one), we expected CBT to be more durable as compared to SSRI and CBT+SSRI. As a result, a fall-off in gains of the combined treatment after medication taper was expected and patients receiving CBT were expected to need less aftercare as compared to the other groups. Overall, the results of the studies in the present thesis do not confirm the context-safety hypothesis. Regarding the need for aftercare, results indicated that a little more CBT+SSRI patients received some form of additional treatment during follow-up as

compared to the patients in the monogroups but the difference was non-significant (CBT+SSRI: 33%, CBT: 16%, SSRI: 21%).

Furthermore, on the outcome effect measures, no fall-of in gains for either treatment modality was observed. Visual inspection of Figure 2 (chapter four) might suggest a temporary detrimental effect of tapering medication (although non significant) followed by a recuperation in-between follow-up 1 and follow-up 2. Results of the Sharp et al.[4] and Barlow et al.[5] studies indicated that treatments incorporating CBT (as monotreatment or combined with drug treatment) may be more durable as compared to treatments not offering CBT. The difference in long-term outcome between the present study and the studies by Barlow et al. and Sharp et al. might be explained by the longer follow-up period (twelve as compared to six months) but more research regarding this matter is needed. The context-safety hypothesis is mainly derived from experimental studies framed within the learning theory paradigm. Explaining present findings within this learning theory bridging the gap between laboratory findings and human pathological anxiety and treatment aimed at ameliorating this anxiety remains a challenge for future studies.[6]

Role of concurrent AG

Out of the 150 patients that started treatment in the present study, 72 patients did not suffer from AG or suffered from mild AG (48%), and 78 patients suffered from moderate or severe AG (52%).

In a meta-analysis,[3] it was concluded that there are no reasons for a different treatment regimen in PD patients without AG as compared to patients with AG. At least two findings from the present thesis are relevant in this respect. First, we found a significant main effect of AG status (no/mild vs. moderate/severe) as predictor

variable for the primary outcome measure PAI Coping (see chapter four) indicating that patients with moderate/severe AG reported less confidence in their ability to cope with future panic attacks as compared to patients without or with only mild AG. Second, regarding rate of improvement, results indicated that among patients with moderate or severe AG, rate of improvement was faster with CBT+SSRI as compared to SSRI and CBT. These findings are in accordance with the findings of De Beurs et al.[7] suggesting the combined treatment to be most beneficial for PD with moderate or severe AG after twelve weeks. Also, Telch et al.[8] found a combined imipramine and exposure treatment most beneficial for severe agoraphobics. These findings are in line with a meta-analysis by Van Balkom et al.[9] which suggests that for PD with AG, a combination of antidepressants with exposure in vivo is the most potent short-term treatment. Consequences for clinical guidelines are discussed in the section clinical recommendations.

Rate of improvement

Regarding rate of improvement (chapter five), a significant decline in frequency of panic attacks was observed during the one year treatment period for each treatment modality. SSRI and CBT+SSRI were both associated with a significant faster rate of improvement on panic frequency as compared to CBT. This is in accordance with the study by Sharp et al. (1996). It was found that the combined fluvoxamine plus CBT group produced significant change earlier as the other treatments. The finding that SSRIs have a more immediate effect as compared to CBT is acknowledged by different authors[10,11] who subsequently fear that this rapid suppression of anxiety may deprive patients of robust safety learning and consequently predicts a stronger return of fear. Based on current findings this fear seems uncalled for.

Cost-effectiveness

The economic evaluation of our data (chapter six) revealed that in all three groups, total costs were largely influenced by costs of the interventions and productivity losses. Furthermore, costs of medication use were substantial for patients in both the SSRI and CBT+SSRI group. When examining the balance between costs and health outcomes, both CBT and CBT+SSRI led to more positive outcomes than SSRI-only. Although CBT was associated with lower costs, assessed health outcomes were slightly more in favor of CBT+SSRI.

7.3 Points of consideration

Six topics will be addressed: dropout, remittance and relapse, no tapers, additional treatment during follow-up, validity of results, and limitations.

Dropout

In the present study, 53 patients (35%) prematurely ended treatment. Note that dropout criteria differ between studies, are often related to completer criteria, and directly influence dropout-, completer- and relapse-rates (see next section) and thereby overall results of a study.

As explicated in chapter four, we applied rather strict definitions of dropouts and completers. In the present study, a patient who received fourteen CBT sessions and subsequently terminated treatment without therapist consent was considered a dropout while in some other studies such a patient would be categorized as a completer. We choose for this definition in order to ensure a homogenous

completer group but recognize that this has increased our number of dropouts.

In chapter three, present dropout rates are compared to the dropout rates derived from the Barlow et al. study.[5] While in the present study the highest dropout rate was observed for CBT-only, in the Barlow et al. study, the highest dropout rate was observed for the anti-depressant only treatment. Based on the observed ES and dropout rates it was concluded that CBT in the present study did not perform worse compared to CBT in other studies (see chapter three) but rather, SSRI and CBT+SSRI performed better.

Remittance and relapse

In the present study, patients were defined remitters when meeting all of the following criteria: free of panic attacks, minimal anticipatory anxiety, and minimal agoraphobia. Subsequently, relapse was defined as no longer meeting remitter criteria at a particular assessment while these criteria were met at a previous assessment. Note that there are no single broad accepted definitions of remittance and relapse in studies on PD. When comparing outcome of different studies, applied definitions of remitter status and relapse therefore have to be taken into account. In the Barlow et al. study for example, relapse is defined as a drop on one particular outcome measure (e.g. the Clinical Global Impression scale). At follow-up, the combined CBT + imipramine treatment was associated with the highest relapse rate; 40%, as compared to 8% for CBT-only and 25% for imipramine-only. In a naturalistic long-term pharmacotherapy study,[12] patients were defined remitters when reporting no panic attacks during an eight-week period. Of the patients that (spontaneously) discontinued medication treatment, 35% still met remitter criteria after three years. In comparison, present findings revealed that at follow-up 2, 48%

of CBT+SSRI, 31% of CBT, and 25% of SSRI patients still met remitter criteria. In a study by Biondi et al.,[13] patients who had achieved remission after drug treatment and received concurrent CBT during follow-up were compared to patients who had achieved remission after drug treatment and subsequently did not receive concurrent CBT during follow-up. Relapse rates were significantly higher among patients who had received medication-only as compared to patients who had received both medication and CBT. Treatment allocation however was based on preference and this seriously limits the validity of these findings.

In sum, while in the Barlow et al. study the combined treatment was found to have the highest relapse rate; in the present study the combined treatment was found to have the highest remitter rate. The latter finding is in line with a naturalistic study[13] who also found the combined treatment to be most durable at follow-up.

Again returning to present findings, although results do not confirm CBT+SSRI and SSRI patients to be more vulnerable for relapse as compared to CBT patients, interestingly, the timing of relapse did differ between treatment modalities. Patients having received SSRI seemed most vulnerable to relapse in-between posttest 1 and posttest 2 (tapering period), patients having received CBT+SSRI seemed most vulnerable to relapse in-between posttest 2 and follow-up 1, and patients having received CBT seemed most vulnerable to relapse in-between follow-up 1 and follow-up 2 (see remitter status in Table 4.4, chapter four). Relapse rates were low in the present study but a trend seems to be that in time, first gains of SSRI, than CBT+SSRI, and finally CBT are prone to abatement. This (non-significant) finding matches the context-safety hypothesis.

No-tapers

Only a small proportion of the patients in the present sample, 16.2%, proved unable to taper medication according to protocol. This suggests that with good therapist guidance and a clear rationale, the vast majority of patients are indeed able to taper their medication. No-taper patients continued to improve and prolonging treatment resulted in additional patients achieving remitter status. Note however, that no-taper patients never reached completer levels; they reported overall higher anxiety and depression levels and felt less confident about their ability to cope with future panic attacks as compared to completers (see chapter four). This lack of self-efficacy may cause these patients to fear taper or may be caused by not-tapering: it is difficult to differentiate between cause and effect in this matter.

Although present findings suggested subsequent improvement in this small group of patients, there is also some evidence suggesting that patients might experience a return of their complaints despite continued treatment. In a study by Simon et al.,[(14)] nearly half of the patients treated with pharmacotherapy (benzodiazepines, antidepressants, or both) who initially achieved remission relapsed within a 24-month follow-up period while pharmacotherapy was continued suggesting that prolonging medication treatment does not completely prevent relapse.

In the present study, medication taper was included in the design and scheduled after nine months of SSRI-use. Some naturalistic studies deal with long-term treatment adherence and spontaneous treatment discontinuation. Understanding why patients spontaneously discontinue drug treatment might be important when long-term treatment adherence is considered essential in preventing relapse and recurrence of symptoms. In several studies, patients are not invited to taper but

rather monitored naturalistically.

In one such naturalistic study,[15] patients received paroxetine for twelve months. After twelve months, they were given the choice to continue for another twelve months or to taper medication. In the latter group, 14% of the patients subsequently relapsed during the follow-up year. Note that patients were not randomized at random but by preference. It was concluded that the extension of paroxetine maintenance treatment from 12 to 24 months did not further decrease the risk of relapse after medication discontinuation.

In a three-year naturalistic study,[16,12] almost 55% of the 326 patients that were followed for three years spontaneously discontinued treatment. The observation that patients discontinue treatment spontaneously attests to the importance of studying post-treatment course. A substantial number of the patients who defaulted from further treatment did so due to achieving symptom remission (36.9%) and only a small portion of patients did so because of side effects. In comparison, in the present study, 24.4 % of all patients who dropped out (this included patients that had received CBT-only) did so because of side effects and no subjects reported symptom remission as a reason for dropout.

Additional treatment during follow-up

In the present study, the number of patients in need of additional treatment during follow-up seems limited although comparison with other studies is difficult as data on this subject is sparse. No data regarding this matter is provided in the Barlow et al. study[5] nor in the other studies included in Table 1.1 (see chapter 1) with the exception of the Sharp et al. study.[4] In the latter study, about half of the patients were in need of additional treatment in between end-point assessment and follow-

up and these were excluded from analysis. In the present study, treatments lasted for one year and perhaps treatment duration contributed to the fact that relatively few patients were in need of additional treatment during follow-up. In a naturalistic follow-up study by De Beurs et al.[1] 77% of the original sample had received some form of additional treatment during a two year naturalistic follow-up. In comparison, this rate was 23% during the twelve month follow-up period for the completer sample in the present study. One possible explanation might be the shorter duration of treatment. Twelve treatment sessions were offered in the study by De Beurs et al. and posthoc, the authors considered this to be an insufficient number of sessions. Regarding CBT however, the assumption that longer treatment duration prevents relapse and thus the need for additional aftercare is at odds with studies reporting that shortening treatment has no detrimental long-term effect.[17] An interesting finding for CBT is that patients having received CBT received less aftercare as compared to patients having received CBT+SSRI and this finding, although not confirmed by other findings, does match the context-safety hypothesis.

Validity of results

The concept of internal validity refers to the extent to which the particular intervention, rather than extraneous influences, can be considered to account for the observed results. Closely connected to internal validity is the concept of treatment integrity: the evaluation of the extent to which treatment was conducted as intended. It might be reasoned that CBT in this matter has more to prove than SSRI. The concept of external validity refers to the extent in which results can be generalized or extended to people, settings, times, measures, and characteristics other than those in this particular experimental arrangement. In our introductory

chapter, we stated that comparing treatments in real-world settings is considered an important endeavour. The present study can be viewed as a hybrid study[18] attempting to move from efficacy toward effectiveness (see chapter one for introduction of these concepts). Clinical randomized trials are usually designed to evaluate short-term clinical outcomes while effectiveness studies are usually designed to evaluate long-term clinical and morbidity outcomes. Some characteristics of effectiveness studies include large(r) study samples, a societal perspective (e.g. collecting cost data), less frequent follow-up assessments (e.g. every few months in stead of weekly), and less clinical detail (e.g. no stringent treatment protocols). Internal and external validity cannot both be optimized in one study. In general, efficacy studies place a higher priority on internal validity while effectiveness studies place a higher priority on external validity.[19]

In designing the present study, decisions were made enhancing external validity and consequently diminishing internal validity. Internal validity was threatened by the absence of blinding. Another threat to internal validity is the fact that no formal treatment integrity checks were applied. Treatment integrity was monitored through detailed forms regarding session content completed by therapists. Important to note at this point is that effect sizes were calculated (see chapter three) and these revealed that the CBT in the present study performed comparable to other studies while the SSRI and CBT+SSRI modalities performed even better as compared to the medication-only treatments and combined treatments in other studies. We can conclude therefore that indeed, treatments were delivered as supposed to and that treatment generally performed as expected.[20] Note that to our knowledge, this is the first study on PD to report between group ES.

A different threat to internal validity is the fact that it was decided to allow patients to use (small doses of) benzodiazepines. This is in accordance with the study

of Barlow et al. In the present sample, 37% of the patients used benzodiazepines at some point during the study (see chapter three for additional findings regarding benzodiazepine use). It was concluded that benzodiazepine use was limited and could not be held accountable for established results.

The present study can be considered highly externally valid. Rather than delivering treatments in specialized anxiety clinics only (like for instance in the Barlow et al. study) the present study was conducted in different settings, including general mental health centers and treatments were delivered by different therapists with different levels of experience (note that CBT treatment in the study by Sharp et al.[4] is delivered by one single therapist). Further, no stringent inclusion criteria were applied and treatments were intended to approximate care as usual. CBT consisted of 21 sessions; although this is more than common in most other trials (see chapter one) this number might actually be more in line with common practice in general mental health centers. Visits concerning pharmacotherapy lasted 20 minutes each. This might be in line with general health care practice but data is limited. Regarding CBT, SSRI and combined treatment regimens; there is a need for collecting naturalistic data concerning treatment length and therapist contact time in general mental health settings.

Limitations

Next to the different limitations already explicated in chapters three to six, some general points deserve additional mentioning. First, different methodologies and corresponding statistical techniques were applied in the different studies included in the present thesis. In chapter three we choose for a completer and ITT analysis. Subsequently, when all data was collected, for the analysis of the long-term results, a

multilevel approach seemed more appropriate.

We have gathered a large amount of data from our participants but in hindsight there are, of course, ideas on additional information that would have been useful. For instance, we could have studied side effects not only in the SSRI and CBT+SSRI modality but also in patients receiving CBT-only. Further, besides gathering data on presence of side effects, the degree to which patients suffer from these side effects would have been interesting as well. This would have contributed to a better understanding on the subject of patients' perspective on treatment acceptance. Also, more information on attribution of effect would have been of value (see section future research).

7.4 Clinical recommendations

With respect to present findings, we want to emphasize that each treatment modality proved effective and participating patients, regardless of which treatment they had received, were highly satisfied with the received treatment at treatment end-point (as indicated by scores on a questionnaire assessing treatment satisfaction). Nevertheless, current findings allow us to draw-up some guidelines in treatment allocation.

Several disadvantages of both monotreatments derive from the data. SSRI as monotreatment was: (1) less cost-effective; (2) associated with smallest remitter rates; and (3) patients reported lower coping scores. Disadvantages for CBT as monotreatment included: (1) highest dropout rate; (2) less remitters as compared to CBT+SSRI; and (3) longer time needed to achieve results similar to the combined treatment. Regarding the combined treatment, CBT+SSRI yielded excellent results up to treatment end-point and gains were preserved throughout the one-year follow-up

period. Advantages of the combined CBT+SSRI treatment as compared to both monotreatments include: (1) highest satisfaction scores; (2) lowest dropout rate; (3) most remitters at follow-up 2; and (4) faster rate of improvement as compared to monotreatments.

Interestingly, CBT treatment in the CBT+SSRI modality did not last longer (as measured in number of received sessions) as compared to CBT treatment in the CBT-only condition: combining treatments may thus result in less CBT sessions thereby enhancing cost-effectiveness.

Taken results of chapters three to six together, we would suggest CBT+SSRI as first-line treatment for PD patients with moderate or severe AG, and CBT as first-line treatment for PD patients without or with only mild AG. Additional clinical points we would like to suggest based on the present study are:

- Regarding the CBT+SSRI treatment, we would like to suggest waning patients from medication while CBT is ongoing. This may require biweekly of monthly CBT booster sessions during tapering.
- Additional benzodiazepines are associated with more cons than pros. Furthermore, present findings suggest that patients can do without.
- SSRIs may be tapered: the general fear of relapse after discontinuation seems uncalled for.
- Providing information and guidance surrounding SSRI use and SSRI taper may contribute to the strength of the combined CBT+SSRI treatment.

In the literature, barriers to treatment accessibility are put forward as a pragmatic argument in favor of SSRI-only. This might be a problem in some countries (e.g. the United States[21]), but is not well supported regarding current general mental health care settings in the Netherlands. Moreover, if limited CBT accessibility was indeed determined, correcting this problem by enhancing CBT availability seems more appropriate than resigning to a less favorite option.

Algorithms derived from the multidisciplinary guidelines from the Netherlands[22] suggest to deliver combined CBT and SSRI treatment as a next step when monotreatment has been only partially successful (see paragraph 1.4.5 of chapter one). Regarding CBT, a distinction is made between exposure in vivo and panic management, e.g. panic control treatment, with the first being especially important when agoraphobic avoidance is present. This distinction might not be useful because in daily clinical practice, as in the CBT protocol used in the present study, both exposure in vivo and so called panic management interventions such as interoceptive exposure and cognitive restructuring are incorporated in most CBT packages.

In discussing clinical recommendations, it is interesting to take into account recent changes in diagnostic criteria as formulated by the American Psychiatric Association (APA). In the latest edition of the DSM, DSM-5 (first released in May 2013), the occurrence of panic attacks can be listed as a specifier that is applicable to all DSM-5 disorders. Further, PD and AG are unlinked in DSM-5. This means that two disorders can be diagnosed: PD and AG each with separate criteria. This might imply that in future, for patient with only PD, CBT would be treatment of first choice and for patient with both disorders, PD and AG, the combined treatment is to be preferred.

7.5 Suggestions for future research

Some of the present findings suggest a detrimental effect of tapering medication (e.g. timing of relapse and additional care during follow-up: see previous sections) but overall, contrary to prior expectations, we did not find evidence for the context-safety hypothesis. Future research might contribute to the understanding of these results. In this light, the concept of attribution of effect may be of interest. Although speculative for now, it may be that context is also defined by degree of experienced self efficacy.[13] When patients receiving drug treatment attribute treatment gains solely or mainly to the drug, this may be associated with a lower self efficacy defining internal context. Medication taper will then result in an internal context shift resulting in loosing safety and increasing vulnerability for relapse. This view would match findings as reported by a study[23] in which drug treatment was combined with exposure or relaxation. It was found that patients who attributed their gains to medication (alprazolam or placebo) reported more withdrawal symptoms and greater loss of gains as compared to patients who attributed their gains to their own efforts during treatment.

In the present study, too little information regarding attribution of effect was available to reliably report this in our outcome studies. However, at each session therapists were asked to rate attribution of effect as expressed by their patients. It was found that at follow-up 1:

- 13.6% of the patients in the CBT+SSRI group attributed effect mainly to the SSRI,
- 40.9 % of the patients in the CBT+SSRI group attributed effect mainly to the CBT and,
- 45.5% of the patients in the CBT+SSRI group attributed effect evenly to both.

Note that patients already had tapered medication at this point. Subsequently, six

month later at follow-up 2 it was found that:

- 5.6% of the patients in the CBT+SSRI group attributed effect mainly to the SSRI,
- 55.6% of the patients in the CBT+SSRI group attributed effect mainly to the CBT and,
- 38.9% of the patients in the CBT+SSRI group attributed effect evenly to both.

For patients having received the combined treatment attribution to medication thus tends to diminish as time progresses and attribution to CBT tends to increase.

Closely related to this subject is the concept of locus of control. In a study by Bakker et al.[24] the Multidimensional Anxiety Locus of Control Scale (MALC) assessed different attributions of the course of PD and yielded one 'internal' and three 'external' (chance, medication, therapist) scales. Patients were treated with cognitive therapy, clomipramine, or paroxetine (see chapter 1, paragraph 1.4.3). Treatment with cognitive therapy resulted in an increase of 'internal' anxiety control orientation, in comparison with antidepressant therapy. Perhaps future research will more firmly establish a differential effect between treatment modalities for PD with respect to attribution of effect and locus of control contributing to a better understanding of involved mechanisms of change.

Present findings advocate a wider implementation of CBT and SSRI simultaneously, as integrated treatment, especially for patients with concurrent moderate or severe AG. No fall-off in gains was observed for CBT+SSRI and this matches the finding of a meta-analysis reported in 2006.[3] The combined treatment should be further investigated with respect to the optimal sequencing of treatments, the optimal duration of medication with respect to CBT, the optimal duration of CBT with respect to medication, and treatment rationales offered to patients in relation to outcome. In the present design, patients tapered medication while receiving ongoing CBT. Future studies might differentiate between (at least) two combined

treatment regimens: tapering medication following CBT discontinuation, and tapering medication while receiving ongoing CBT. Although the latter treatment modality might intuitively be accredited with relapse prevention, data corroborating this is not present up to date.

With respect to CBT; the present findings regarding rate of improvement raise the question if interventions within CBT can be optimized in order to set in change sooner e.g. by changing the order of interventions or by intensifying home-work in the first phase of treatment. In the last twenty years, there have been relatively few innovations in CBT protocols[25]: these may however be necessary with respect to timing of response. As an example of new innovations, pilot studies are being conducted in which coping skills are added to exposure therapy in the hope of improving outcome.[26]

In the present design, the first assessment was after nine months of treatment. Future studies should evaluate treatments earlier in time. There is evidence that continuing treatment in patients who in the early phase fail to respond is less effective.[27] Also, evidence from an open trial on CBT corroborates the importance of early treatment evaluation allowing clinicians to consider alternative treatment strategies early in treatment.[28]

Further, the follow-up period might be extended; twelve months is (albeit longer than in most clinical trials) too short from an effectiveness perspective. Finally, patients may be monitored more repeatedly. In the same manner as frequency of panic attacks was studied in chapter five, process oriented studies could clarify course in time regarding different PD morbidity aspects.

In conclusion

PD is a well treatable disorder and patients were satisfied with treatment regardless whether they had received SSRI, CBT or CBT+SSRI. In the long-term and especially for patients with concurrent moderate or severe AG, the combined CBT+SSRI treatment modality might be recommended as the treatment of choice being cost-effective and yielding results early in treatment with long-lasting effect. Contrary to some previous findings, in the present study the combined treatment was found to have no disadvantages on the long-term after medication taper. Further inquiry into involved mechanisms of action might shed new light on the proposed context-safety hypothesis and ultimately result in even more effective treatments.

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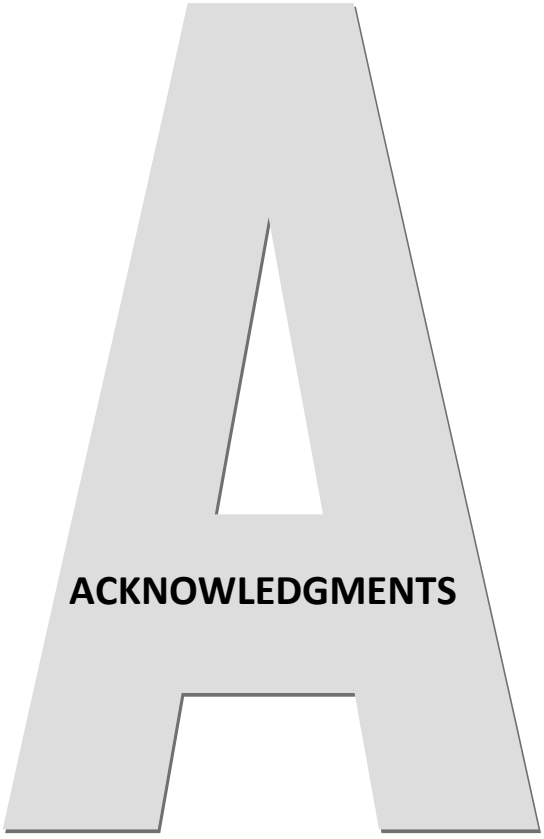

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SAMENVATTING

DE BEHANDELING VAN PANIEKSTOORNIS

PSYCHOTHERAPIE, FARMACOTHERAPIE OF DE COMBINATIE VAN BEIDE?

Nederlandse samenvatting

Inleiding

Het doel van het onderzoek beschreven in dit proefschrift is een bijdrage leveren aan het optimaliseren van de behandeling van paniekstoornis met of zonder agorafobie. Het ondergaan van een paniekaanval is een bijzonder nare ervaring. Plotseling, zonder duidelijke aanleiding, treedt er angst op waarna de angst snel oploopt en een piek bereikt. Lichamelijke sensaties die optreden zijn bijvoorbeeld hartkloppingen, trillen, duizeligheid, een versnelde ademhaling en een druk op de borst. Tijdens een paniekaanval worden deze sensaties doorgaans als gevaarlijk geïnterpreteerd. Mensen kunnen bijvoorbeeld denken dat ze stikken, een hartaanval krijgen, flauwvallen, de controle verliezen of gek worden. Niet iedereen die wel eens een paniekaanval heeft ervaren, ontwikkelt een paniekstoornis. Mensen met een paniekstoornis zijn ook tussen aanvallen door bijna voortdurend bang voor volgende aanvallen of bezorgd over de gevolgen van aanvallen. Als er daarnaast sprake is van vermijding van situaties of plaatsen waar een volgende aanval zou kunnen optreden spreken we van agorafobie. Paniekstoornis kan dus zowel met als zonder agorafobie voorkomen. Paniekstoornis wordt behandeld met psychofarmaca of met psychotherapie en soms ook met beide. Als er gekozen wordt voor farmacotherapie is een behandeling met een SSRI eerste keus; een antidepressivum wat bij zowel depressie als angst wordt voorgeschreven (SSRI staat voor ‘selective serotonin reuptake inhibitor’. In het Nederlands: ‘selectieve serotonine heropname remmer’). Wat psychotherapie betreft is cognitieve gedragstherapie (CGT) eerste keus.

In **hoofdstuk 1** van dit proefschrift wordt onder andere een overzicht gegeven van bestaande behandelvormen en beschikbare empirische evidentie. Voor beide monotherapieën, CGT en SSRI, geldt dat er veel onderzoek gedaan is naar de werkzaamheid op kortere termijn. Onderzoek naar de werkzaamheid op langere termijn is veel minder vaak uitgevoerd. Wat betreft farmacotherapie is er bovendien behoefte aan meer informatie over het behoud van effect na het afbouwen van de medicatie. De grootste lacune bestaat op het gebied van onderzoek naar de effectiviteit van de combinatiebehandeling waarbij patiënten gelijktijdig een SSRI en CGT ontvangen. Er zijn maar weinig studies uitgevoerd waarin SSRI, CGT en de combinatie van beide, binnen hetzélfde onderzoek werden vergeleken. Uit onderzoek tot op heden blijken de verschillende behandelvormen allen effectief en zijn er daarnaast kleine verschillen gevonden. Zo wordt er verondersteld dat patiënten die de combinatiebehandeling hebben ontvangen na het staken van de medicatie mogelijk gevoeliger zijn voor terugval in vergelijking met patiënten die alleen een psychologische behandeling hebben ontvangen voor hun klachten. Dit zou verklaard kunnen worden vanuit de zogenoemde **context–veiligheid hypothese:** als veiligheid wordt aangeleerd in de context van medicatiegebruik zou die veiligheid wellicht komen te vervallen in een nieuwe context ontstaan na het afbouwen van de medicatie. Experimenteel onderzoek op het gebied van aan- en afleren van angst biedt enige ondersteuning voor deze hypothese maar het is nog te vroeg om uitspraken te kunnen doen met betrekking tot klinisch onderzoek bij patiënten met paniekstoornis.

In **hoofdstuk 2** wordt het onderzoek zoals beschreven in dit proefschrift nader geïntroduceerd. Het betreft een zogenaamde RCT: een Randomized Clinical Trial. Proefpersonen mochten niet zelf kiezen welke behandeling zij wilden ontvangen maar werden toegewezen aan één van de behandelcondities door middel van loting. Enkele uitgangspunten bij het opzetten van het onderzoek waren:

- Het onderzoeken van CGT, SSRI en de combinatiebehandeling (CGT+SSRI) binnen één onderzoeksdesign.
- Het onderzoeken van de effectiviteit ook op langere termijn en ook na staken van de medicatie.
- Patiënten zonder agorafobie maar ook met (lichte, matige, of ernstige) agorafobie deel laten nemen om meer zicht te krijgen op de rol van agorafobie in de behandeling van paniekstoornis.
- Het nastreven van een goede externe validiteit; dat wil zeggen dat we de omstandigheden waaronder behandeling plaatsvond zoveel mogelijk wilden doen lijken op de gangbare klinische praktijk.

Deelnemers aan het onderzoek waren allen patiënten met paniekstoornis met of zonder agorafobie. Zij werden behandeld in elf verschillende instellingen in Nederland. De criteria die gehanteerd werden bij de inclusie worden in hoofdstuk 2 beschreven alsook de gebruikte meetinstrumenten en protocollen. Proefpersonen werden toegewezen aan één van drie behandelcondities: CGT, SSRI, of CGT+SSRI. Voor iedere deelnemer duurde het onderzoek twee jaar: het eerste jaar bestond uit de behandeling, het tweede jaar was een follow-up jaar. Er waren vijf meetmomenten: voorafgaand aan de behandeling, na negen maanden behandeling (terwijl ingesteld op een adequate dosering van de SSRI in het geval van SSRI gebruik), na afloop van de behandeling (na het staken van de CGT en / of na het afbouwen van de SSRI), en zes en twaalf maanden na het staken van de behandeling

(de follow-up metingen). Metingen bestonden eruit dat proefpersonen geïnterviewd werden en dat hen gevraagd werd diverse vragenlijsten in te vullen.

De behandeling met CGT besloeg 21 sessies en patiënten kregen uitleg over paniekstoornis en de behandeling, gevolgd door interoceptieve exposure, cognitieve therapie en exposure in vivo. Exposure is een ander woord voor blootstelling. Bij interoceptieve exposure worden mensen blootgesteld aan de interne lichamelijke sensaties die op kunnen treden tijdens paniek. Bij exposure in vivo gaan mensen oefenen in het opzoeken van situaties en het verblijven op plaatsen die ze uit angst voor volgende paniekaanvallen mogelijk liever vermeden. Cognitieve therapie richt zich op het veranderen van de angst opwekkende gedachten en opvattingen (cognities) die mensen er op na houden.

De behandeling met een SSRI bestond uit negen behandelcontacten. Proefpersonen kregen uitleg over paniekstoornis en de behandeling en werden ingesteld op een van vijf SSRIs: fluvoxamine, sertraline, fluoxetine, paroxetine en citalopram. Na ongeveer negen maanden werd de SSRI weer langzaam afgebouwd zodat proefpersonen aan het einde van het behandeljaar medicatievrij waren. Proefpersonen die geloot werden in de CGT+SSRI groep ontvingen zowel CGT als SSRI. Deze behandelingen werden gegeven door twee verschillende behandelaars en liepen parallel aan elkaar.

Het doel van het onderzoek was een bijdrage leveren aan de verdere optimalisering van de behandeling van paniekstoornis. Vragen die we onder andere graag wilden beantwoorden waren: zijn de behandelingen effectief? Is er verschil tussen de drie behandelvormen? Vinden we aanwijzingen voor de context-veiligheid hypothese? Blijft het effect van behandeling behouden na het staken van de CGT en / of SSRI? Is de aanwezigheid en de ernst van de agorafobie van invloed op het therapieresultaat? Is er verschil tussen de behandelingen met betrekking tot het

tempo waarin verbetering optreedt? Is er een verschil tussen de behandelingen met betrekking tot de kosten die ermee gemoeid zijn in relatie tot hun effectiviteit?

(Differentiële) therapie effecten

In hoofdstukken 3 en 4 worden de resultaten beschreven van het effectiviteitsonderzoek.

In **hoofdstuk 3** worden een aantal kenmerken van de onderzoekgroep gepresenteerd. In totaal zijn er 150 patiënten met paniekstoornis gestart met de behandeling. Deze groep bestond voor ongeveer de helft uit vrouwelijke proefpersonen (54.7%). Ongeveer de helft van de proefpersonen had geen of slechts milde agorafobie, bij de andere helft (52%) was er sprake van matige of ernstige agorafobie. Hoofdstuk 3 presenteert de resultaten van de meting na negen maanden toen de CGT gaande en / of de SSRI nog niet afgebouwd was. Er werd gevonden dat op dat moment alle drie de behandelvormen effectief waren; dat wil zeggen dat proefpersonen in alle drie de groepen een significante daling van hun klachten rapporteerden. CGT+SSRI bleek op een aantal maten effectiever dan CGT terwijl er niet veel verschil geconstateerd werd tussen CGT+SSRI en SSRI.

De effectgroottes van de drie behandelmodaliteiten werden berekend en vergeleken met effectgroottes zoals gerapporteerd in, of afgeleid uit, vergelijkbare onderzoeken. We wilden zodoende een uitspraak kunnen doen over de kwaliteit van de CGT, SSRI en CGT+SSRI binnen ons onderzoek. We vonden dat de CGT minstens zo goed presteerde als de CGT in andere onderzoeken en dat de SSRI en de combinatiebehandeling zelfs hógere effectgroottes opleverden in vergelijking met deze behandelmodaliteiten in andere onderzoeken.

Hoofdstuk 4 presenteert de resultaten tot en met de laatste follow-up aan het

einde van het tweede jaar. Naast de differentiële therapie effecten werd ook de relatie tussen therapie effect en zeven voorspellende variabelen onderzocht. Een aantal patiënten (35% van de onderzoeksgroep) stopte om verschillende redenen met de behandeling en / of het onderzoek gedurende het eerste behandeljaar. Hier vallen ook patiënten onder die bijvoorbeeld na een aantal weken CGT tevens begonnen met een SSRI behandeling; als zij geloot waren in de CGT groep werden ze als 'uitvallers' beschouwd in de analyses. Het aantal uitvallers was niet significant verschillend tussen de drie behandelgroepen. Een klein aantal van de patiënten die volgens protocol een SSRI ontvingen, hebben deze SSRI aan het einde van het behandeljaar niet af kunnen of willen bouwen. Deze 'niet afbouw' groep (14 proefpersonen) werd in de analyses vergeleken met de 'uitvalgroep' (53 proefpersonen) en de 'completer' groep (83 proefpersonen). Deze laatste groep was de grootste; het betreft de patiënten die de therapieën volgens protocol hadden afgerond. Patiënten in de 'niet afbouw' groep rapporteerden meer angst- en depressieve klachten vergeleken met patiënten in de 'completer' groep.

Uit de resultaten voor de completer patiënten bleek opnieuw dat patiënten in alle drie de behandelgroepen significant waren verbeterd. De combinatiebehandeling, CGT+SSRI, had als voordeel dat verbetering sneller optrad in vergelijking met alleen CGT terwijl deze laatste als voordeel had dat er geen bijwerkingen aan verbonden waren en iets korter duurde in tijd.

Gebaseerd op de context-veiligheid hypothese zouden we verwachten dat proefpersonen in de CGT+SSRI groep méér nabehandeling nodig zouden hebben in vergelijking met proefpersonen in de CGT groep. Samenhangend zou terugval na het afbouwen van de medicatie tot uiting kunnen komen door een terugkeer of verergering van klachten of een toename van het aantal paniekaanvallen. We vonden in onze resultaten over het algemeen geen bevestiging voor de context-

veiligheid hypothese. Meer dan de helft (64%) van de 'completer' proefpersonen zocht gedurende het follow-up jaar géén aanvullende hulp. De proefpersonen die wel hulp zochten tijdens het follow-up jaar bleken ongeveer gelijk verdeeld over de drie behandelcondities: er waren weliswaar iets meer proefpersonen in de CGT+SSRI groep die nabehandeling nodig hadden maar het verschil bleek niet significant. De gunstige therapie effecten werden bovendien behouden tot en met het laatste meetmoment. Er vond dus over het algemeen geen terugval plaats gedurende het follow-up jaar nadat de behandelingen gestaakt waren.

Een van de voorspellende variabelen was 'type instelling'; het bleek voor het therapie-effect niet uit te maken in welk type instelling (bijvoorbeeld een onderzoeksinstelling of een GGZ instelling) een proefpersoon behandeld werd. Dit is een belangrijke bevinding want het betekent dat de behandelingen die oorspronkelijk vanuit een onderzoekssetting ontwikkeld zijn goed toepasbaar blijken in de klinische praktijk. Wat betreft de aanwezigheid van agorafobie bleek er alleen een relatie te zijn met de mate waarin patiënten vertrouwen hadden in hun vermogen om met toekomstige paniekaanvallen om te gaan: patiënten met matige en ernstige agorafobie hadden hier minder vertrouwen in vergeleken met patiënten zonder of met milde agorafobie. Het gebruik van additionele benzodiazepines (medicijnen die angst onderdrukken waarbij het effect snel optreedt en ook relatief snel weer verdwijnt) werd binnen het huidige protocol niet aangemoedigd maar in minimale dosering toegestaan. Meer dan de helft van de proefpersonen (63%) gebruikte op geen enkel moment gedurende het onderzoek benzodiazepines. Proefpersonen die gedurende de behandeling dagelijks benzodiazepines bleven gebruiken bleken zich minder gezond te voelen en hadden minder vertrouwen in hun vermogen om met toekomstige paniekaanvallen te gaan in vergelijking met proefpersonen die geen of slechts heel af en toe benzodiazepines gebruikten.

Snelheid van verbetering

In **hoofdstuk 5** wordt een studie beschreven naar de snelheid van verbetering binnen de verschillende behandelgroepen. De deelnemende patiënten werd gevraagd om gedurende het eerste behandeljaar iedere paniekaanval die optrad te noteren. Dit leverde informatie op over de frequentie van paniekaanvallen en het verloop van die frequentie gedurende het behandeljaar. Als maat voor snelheid van verbetering kozen we de afname in de frequentie van gerapporteerde paniekaanvallen. Alle drie de groepen, CGT, SSRI en CGT+SSRI lieten een significante daling van het aantal paniekaanvallen zien tijdens het behandeljaar. Na twaalf maanden kwamen paniekaanvallen niet of nauwelijks meer voor ongeacht welke behandeling de patiënten hadden ontvangen. We vonden een duidelijk verschil in tempo van verbetering: de frequentie van paniekaanvallen nam in de SSRI en in de CGT+SSRI groep significant sneller af in vergelijking met de CGT groep. Het verschil tussen SSRI en CGT+SSRI bleek niet significant. Het aantal paniekaanvallen nam niet toe tijdens of na het afbouwen van de medicatie in de SSRI en CGT+SSRI groepen. De aanwezigheid van agorafobie bleek niet voorspellend voor het algemene verloop in frequentie van paniekaanvallen. Wel bleek dat patiënten met matige of ernstige agorafobie die een van beide monotherapieën ontvingen een kleinere afname van paniekaanvallen lieten zien in vergelijking met patiënten zonder of met milde agorafobie. Ook bleek dat patiënten met matige of ernstige agorafobie een snellere afname van het aantal paniekaanvallen lieten zien als zij CGT+SSRI ontvingen in vergelijking met patiënten met matige of ernstige agorafobie die een van beide monotherapieën ontvingen.

Kosteneffectiviteit

In **hoofdstuk 6** worden de resultaten van een studie naar de kosteneffectiviteit van de drie behandelmodaliteiten beschreven. Psychiatrische aandoeningen gaan gepaard met maatschappelijke kosten. Naast de directe kosten verbonden aan de behandeling van een aandoening zijn er ook indirecte kosten bijvoorbeeld als gevolg van productieverlies wanneer patiënten in de ziektewet terechtkomen. De laatste jaren heeft onderzoek naar kosteneffectiviteit een grotere nadruk gekregen in de wetenschappelijke literatuur. Dit past bij de maatschappelijke ontwikkelingen van de noodzaak van kostenbeheersing en het moeten verantwoorden van interventies op het gebied van de (geestelijke) gezondheidszorg richting verzekeringsmaatschappijen. Een interventie is kosteneffectief, doelmatig, als de kosten die ermee gepaard gaan in verhouding staan tot de effecten van de interventie.

In het geval van paniekstoornis met of zonder agorafobie is dergelijk onderzoek nog maar weinig uitgevoerd en in het bijzonder was er nog niet eerder onderzoek gedaan waarbij naast de directe kosten ook de indirecte kosten werden vergeleken. In de kosteneffectiviteitanalyse beschreven in hoofdstuk 6 werd als therapie uitkomstmaat de score op de HAM-A gebruikt (HAM-A: Hamilton Anxiety Rating Scale). Daarnaast werd uitgebreide informatie verzameld over zowel directe als indirecte kosten door middel van een gestructureerd interview. Deze informatie werd verzameld tijdens de vijf eerder beschreven meetmomenten gedurende de twee jaar dat proefpersonen deelnamen aan het onderzoek. Het bleek dat er over de twee jaren heen geen statistisch significante verschillen gevonden werden tussen de drie behandelmodaliteiten met betrekking tot kosten en therapie uitkomsten. Een onderlinge vergelijking liet zien dat CGT en CGT+SSRI kosteneffectiever bleken in

vergelijking met SSRI als monotherapie. CGT ging gepaard met iets lagere kosten terwijl CGT+SSRI gepaard ging met een iets groter therapie effect. Welke van deze twee behandelingen de voorkeur zou moeten verdienen is van vele factoren afhankelijk.

Conclusie

In het afsluitende hoofdstuk van dit proefschrift, **hoofdstuk 7**, worden de resultaten van de beschreven studies samengevat en gerelateerd aan eerder onderzoek. Aansluitend worden er een aantal discussiepunten besproken. Tot slot worden er aanbevelingen gedaan met betrekking tot de klinische behandelpraktijk en toekomstig onderzoek.

Zowel CGT als SSRI als de combinatiebehandeling, CGT+SSRI, blijken effectieve behandelingen voor paniekstoornis met of zonder agorafobie. De positieve effecten van therapie werden behouden na het staken van de behandeling tot en met de laatste follow-up. Er werden geen duidelijke aanwijzingen gevonden voor de context-veiligheid hypothese. Dat wil zeggen dat er geen nadelige effecten van het afbouwen van de medicatie gevonden werden. Dit is een belangrijke bevinding die uit eerder onderzoek nog niet zo duidelijk naar voren was gekomen. Patiënten die SSRI of CGT+SSRI ontvingen verbeterden sneller (als gemeten in frequentie paniekaanvallen) in vergelijking met patiënten die alleen CGT ontvingen. Vanuit een kosteneffectiviteitsperspectief zouden CGT en CGT+SSRI de voorkeur verdienen boven alleen SSRI. Bij het toewijzen van behandeling aan patiënten zal in de toekomst het wel of niet aanwezig zijn van matige of ernstige agorafobie mogelijk een factor van belang zijn. Er werd namelijk gevonden dat patiënten met matige of ernstige agorafobie sneller verbeterden op de combinatiebehandeling in vergelijking

met de monotherapieën. Andere voordelen verbonden met de combinatiebehandeling waren dat CGT+SSRI geassocieerd was met de hoogste tevredenheidsscore[6], het laagste uitval percentage en het hoogste percentage remitters[7].

Omdat er nog maar weinig onderzoek gedaan is zoals dit, is het belangrijk dat huidige bevindingen gerepliceerd gaan worden. Die herhaling is nodig zodat we met meer zekerheid klinische aanbevelingen kunnen doen. Het zou zinvol zijn om daarbij nog meer patiënten te betrekken en deze nog langer te volgen dan de twee jaar in de huidige onderzoeksopzet. Met betrekking tot de combinatiebehandeling is bovendien nader onderzoek gewenst naar de meest optimale volgorde, duur en fasering van de verschillende onderdelen en de uitleg die patiënten aangeboden krijgen over deze behandeling. Vervolgonderzoek zou mogelijk ook meer ideeën kunnen opleveren over hoe huidige resultaten te verklaren zijn in het licht van bevindingen vanuit experimenteel onderzoek naar het aan- en afleren van angst. Eenvoudig gesteld: hoe verklaren we dat er wel aanwijzingen gevonden zijn voor de context-veiligheid hypothese in experimenteel onderzoek bijvoorbeeld met muizen maar niet in huidig klinisch onderzoek bij mensen?

Ondanks het besef dat voorzichtigheid geboden is en het nog te vroeg is voor definitieve conclusies willen we toch een poging doen de huidige resultaten te vertalen naar aanbevelingen voor de klinische praktijk. In hoofdstuk 7 worden daarom een aantal suggesties gedaan. Er wordt voorgesteld dat voor patiënten met paniekstoornis zonder of met milde agorafobie een CGT behandeling eerste keus is. Voor patiënten met paniekstoornis en matige of ernstige agorafobie is CGT+SSRI de eerste keus behandeling; deze blijkt kosteneffectief en is snel en blijvend effectief.

[6] Zoals gemeten op een vragenlijst over de mate van tevredenheid met de ontvangen behandeling die patiënten, na afloop van de behandeling, hebben ingevuld.

[7] Een 'remitter' was een proefpersoon die aan een aantal verbetercriteria voldeed zoals uitgelegd in hoofdstuk 4.

Wat betreft het voorschrijven van additionele benzodiazepines aan patiënten met paniekstoornis suggereren de resultaten van huidig onderzoek dat dit niet nodig is en dat dagelijks benzodiazepinegebruik bovendien geassocieerd is met een aantal nadelen. In de klinische praktijk zijn artsen soms aarzelend om SSRIs af te bouwen na het bereiken van volledige remissie. Huidige resultaten ondersteunen de opvatting dat SSRIs wel degelijk afgebouwd kunnen worden: behandeling hoeft niet te worden voortgezet uit angst voor terugval na afbouwen. Het is mogelijk verstandig om de SSRI af te bouwen terwijl de CGT nog gaande is. Het is tevens aan te bevelen patiënten goed voor te lichten over en te begeleiden in het afbouwen van de SSRI.

In tegenstelling tot enkele eerdere bevindingen vonden wij op langere termijn geen nadelige effecten van de combinatiebehandeling CGT+SSRI. Toekomstig onderzoek zal mogelijk nieuwe inzichten opleveren met betrekking tot de context-veiligheid hypothese, werkingsmechanismes die een rol spelen in therapie-effecten en de wijze waarop de combinatiebehandeling het beste aangeboden kan worden. Zo zal wetenschappelijk onderzoek bij blijven dragen aan de verdere optimalisering van de behandeling van paniekstoornis.

DANKWOORD

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